# Neurology

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MARCH--1961

Volume 11 - Number 3

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1. Lehrer, H. W., et al.: Northwest Med. 75:1249, 1955.
2. Smith, Richard T.: New York Med. 8:16, 1952.

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1. Critchley, M.: **British, M. J.**, 2:1214 (Nov. 15) 1958.
2. England, A. C., and Schwab, R. S.: **A.M.A. Arch. Int. Med.** 104:439 (Sept.) 1959.
3. Judah, L., Murphree, O., and Seager, L.: **Am. J. Psychiat.** 115:118 (June) 1959.
4. Pennington, V. M.: **M. Times** 87:1432 (Nov.) 1959.



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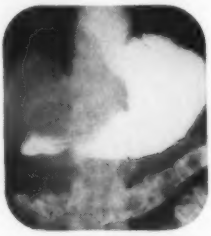

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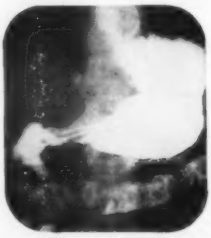

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*Volume 11* **Neurology** *Number 3*

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MARCH 1961 • *Contents*

Complications of Carotid Manipulation ..... 185
CAPT. JOHN R. CALVERLEY, M.C., U.S.A.F., and CLARK H. MILLIKAN, M.D.

Cerebrovascular Effects of Topically Applied Serotonin in the Cat ..... 190
R. B. RAYNOR, M.D., J. G. MC MURTRY, M.D., and J. L. POOL, M.D.

Possible Mechanisms of Action of Hypertonic Urea in Reducing Intracranial Pressure ..... 196
THOMAS W. LANGFITT, M.D.

Pupillary Abnormalities in Myasthenia Gravis: Report of a Case ..... 210
AUGUSTO GENTIL BAPTISTA, M.D., and HAROLDO SILVA e SOUZA, M.D.

Autonomic Representation in the Human Orbitotemporal Cortex ..... 214
J. M. VAN BUREN, M.D., C. A. BUCKNAM, M.D., and W. L. PRITCHARD, M.D.

Delayed Postoperative Hemorrhage from Intracranial Aneurysm after Craniotomy for Tumor ..... 225
PATRICK E. TAYLOR, M.D.

Identification and Quantitation of *N*-Acetylneuraminic Acid in Human Cerebrospinal Fluid ..... 232
RUTH KERR JAKOBY, M.D., and LEONARD WARREN, M.D., Ph.D.

Histopathology of the Bing-Neel Syndrome ..... 239
ROBERT EDGAR, M.D., and THOMAS F. DUTCHER, M.D.

(Continued on following page)

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# Contents—*Continued*

Adrenocortical Function in Epilepsy:
II. The Role of Corticosterone in the Mechanism and Management of Epilepsy ..... 246
PATRICK F. BRAY, M.D., VINCENT C. KELLEY, M.D., Ph.D., GERARDO ZAPATA, M.D., and ROBERT S. ELY, M.D.

Effect of Intrathecal Hydrocortisone on Advanced Adhesive Arachnoiditis and Cerebrospinal Fluid Pleocytosis: An Experimental Study 251
SHAUL FELDMAN, M.D., and ALBERT J. BEHAR, M.D.

Dilantin in the Treatment of Lightning Pains ..... 257
LT. JOSEPH B. GREEN, M.C., U.S.N.R.

Observations on Ceruloplasmin and Methods for Its Estimation ..... 259
SEAN O'REILLY, M.D.

Treatment of Epilepsy with $\alpha$-ethyl-$\alpha$-methylsuccinimide (P.M. 671) ..... 266
NEIL GORDON, M.D., M.R.C.P.

Training Program in Pediatric Neurology ..... 269

Program of the American Academy of Neurology Thirteenth Annual Meeting ..... 270

## INFORMATION FOR *Authors*

NEUROLOGY, the official publication of the American Academy of Neurology, has been instituted to provide a medium for prompt publication of articles dealing with neurology and its cognate fields and to stimulate individual investigation in these various fields.

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1. Schwab, R. S. and England, A. C.: *J. Chron. Dis.* 8:488 (Oct.) 1958.
2. Kruse, Walter K.: *Dis. Nerv. System* 21:80 (Feb.) 1960.
3. Schwab, R. S.: *Geriatrics* 14:545 (Sept.) 1959.
4. Doshay, L. J., *et al.*: *J.A.M.A.* 160:348 (Feb. 4) 1956.


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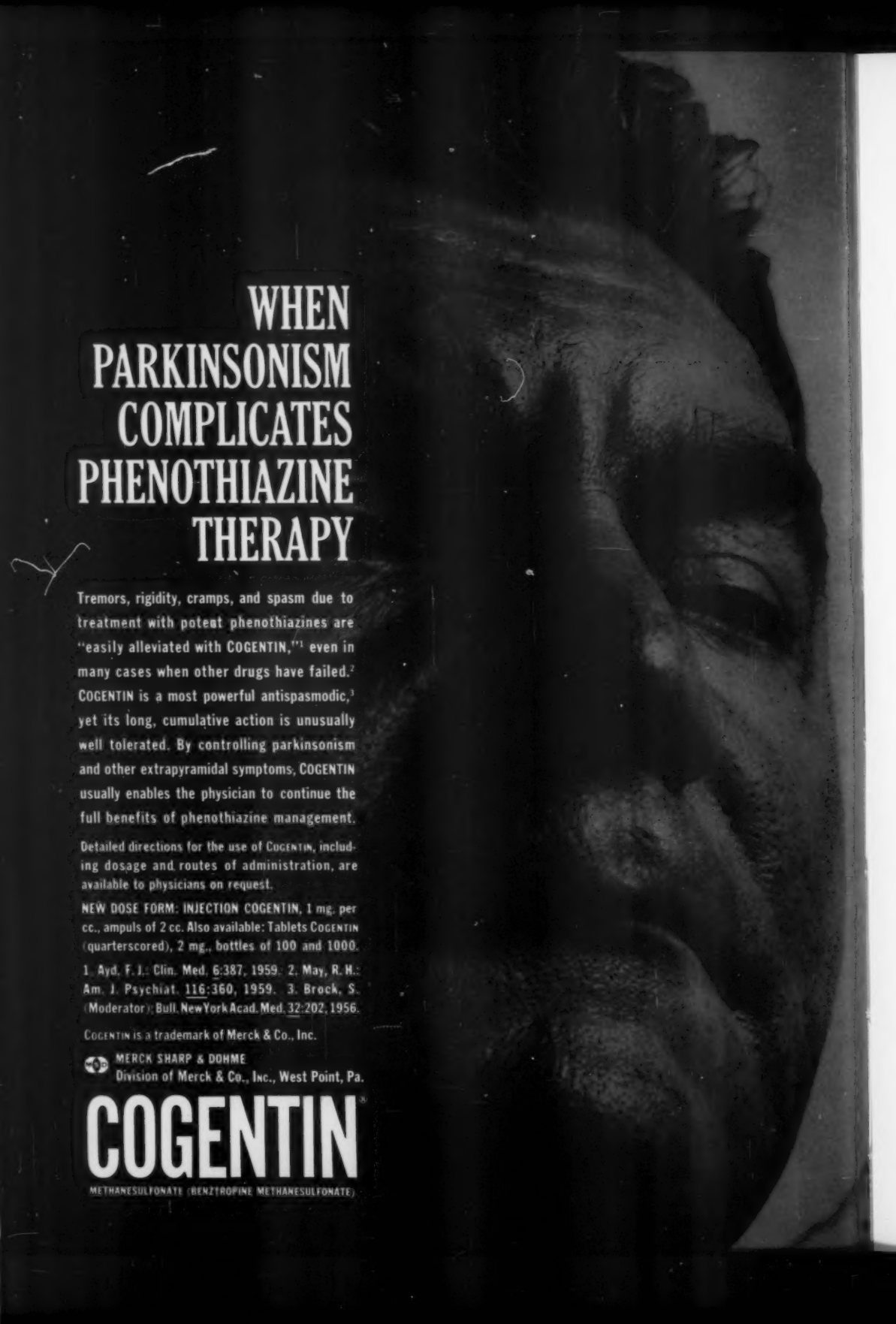

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*K. R. Magee and M. R. Westerberg, **Neurology**, 9:348, 1959.

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# Complications of carotid manipulation

Capt. John R. Calverley, M.C., U.S.A.F., and
Clark H. Millikan, M.D.

PALPATION, massage, and compression of the carotid arteries in the neck are commonly considered to be innocuous procedures. In practice, massage often means compression. In our experience, such manipulation of the carotid arteries has produced serious complications. It is our purpose to report 4 such instances and to discuss the pathogenesis of these complications.

Interest in the effects of manipulation of the carotid arteries is not new. When the ancients named the main vessels to the brain, they chose "karotis," from the Greek word meaning "deep sleep," because they recognized the effects of external pressure on these vessels.[1] The ancient Assyrians reportedly used carotid compression as a means of analgesia in their rites of circumcision. Parry[2] in 1799 detected cardiac slowing from pressure on the carotid arteries.

Weiss and Baker[3] in 1933 clearly outlined the clinical syndromes associated with hyperactivity of the carotid sinus. They described faintness, syncope, and convulsive movements occurring as a result of carotid massage but detected no irreversible neurologic changes in the patients tested. After it was recognized that, occasionally, patients have spontaneous episodes of syncope because of hypersensitivity of the carotid sinus, some physicians massaged the carotid sinus of every patient they examined. Not until 1941 was it recorded that irreversible neurologic damage could result from this maneuver. Marmor and Sapirstein[4] reported on a patient 53 years old whose pulse slowed immediately after compression of the right carotid sinus. This was followed in a few seconds by generalized clonic twitching and syncope. The syncope lasted about ten seconds, and the patient then seemed perfectly normal. Several minutes later, he became unresponsive and manifested weakness of the limbs of the right side. Six hours later, he had spasticity of all limbs. At necropsy, there were recent hemorrhagic infarcts of both frontal lobes. The vessels of the circle of Willis were moderately stenotic.

Askey[5] in 1946 reported several examples of untoward reactions from carotid-sinus stimulation that were observed by members of the California Heart Association. Hemiplegia de-

From the Section of Neurology, Mayo Clinic and Foundation, Rochester, Minn.

Capt. Calverley is on assignment to the Mayo Foundation. The contents of this article are the personal views of the authors and are not to be construed as statement of official Air Force policy nor as Air Force endorsement of any commercial product described.

Read at the twelfth annual meeting of the American Academy of Neurology, Miami, April 30, 1960.

veloped in 8 of the patients, and, in each instance, the weakness was on the side opposite the manipulated carotid artery. In 6 of these patients, weakness developed while the artery was manipulated; 1 patient was free of symptoms for ten to fifteen minutes after cessation of any examination of the neck and then manifested hemiplegia. In 1 patient, weakness developed the day following examination. In at least 2 of the patients described, systemic blood pressure or heart rate was not altered during manipulation of the neck.

Zeman and Siegal[6] undertook a study to confirm the impression that hypersensitivity of the carotid sinus was common in the aged. They tested 188 elderly men and women. The last subject in their series, an 83-year-old man, had no alteration in blood pressure or heart rate and no symptoms as pressure was applied for fifteen seconds to the right and then to the left carotid sinus. Several minutes after the testing, however, paralysis of the right upper limb developed. Among others who have reported serious complications of manipulation of the carotid arteries are Levine,[7] Rose,[8] and Webster and Gurdjian.[9]

In recent years, at least 4 patients seen at the Mayo Clinic had severe neurologic defects coincident with manipulation of the carotid arteries in the neck.

## REPORT OF CASES

**Case 1.** A 35-year-old man was given massage for mild stiffness of the neck. While the right side of the neck was being palpated, he suddenly experienced weakness of the left arm and leg. This weakness was so severe that he was unable to stand or bring his left hand to his face. Apparently, the fingers of the left hand were completely paralyzed for a short time. He was immediately hospitalized, and from that time he began to improve.

He was first seen at the Mayo Clinic two weeks after onset of his disability. Neurologic examination disclosed slight weakness of the left side of his face and of the grip of his left hand. He tended to drag the left foot when he walked. Muscle-stretch reflexes were hyperactive on the left side, and the Babinski response was questionably present on that side. The rate of alternate motion of the hand and foot on the left was slowed. Diastolic pressure in the retinal artery was measured as 50 mm. Hg in each eye. The clinical diagnosis was cerebral infarction in the region of the internal capsule on the right as a result of carotid palpation.

Laboratory findings were urine, normal; hemoglobin, 16 gm. per 100 cc. of blood; leukocyte count, 6,900 per cubic millimeter; and serologic reaction for syphilis, negative.

Roentgenographic examination of the head, thorax, and cervical portion of the spinal column gave normal results. Electrocardiographic and electroencephalographic findings were within normal limits.

The patient was hospitalized for seven days and received physical therapy. His condition improved significantly, and he was able to resume work three weeks after leaving the hospital.

**Case 2.** A 54-year-old woman came to the Mayo Clinic because of swelling in the right side of her neck. She had had increased arterial blood pressure for several years. On examination, her blood pressure was 220/110. A moderately firm, pulsating mass was noted just inferior and posterior to the angle of the right mandible. The diagnosis of carotid-body tumor was made.

Laboratory findings were urine, normal; blood hemoglobin, 15.1 gm.; erythrocyte count, 4,930,000 and leukocyte count, 6,800 per cubic millimeter; true blood sugar, 96 mg. per 100 cc.; and serologic reaction for syphilis, negative.

Electrocardiographic findings were normal.

At operation, a carotid-body tumor (chemodectoma) was removed; it was necessary to manipulate the right internal carotid artery, but it was not occluded even for a few seconds. When the patient awoke, she had a complete left hemiplegia, which also involved the face, and left homonymous hemianopsia. The muscle-stretch reflexes were decreased on the left, and the Babinski response was present on that side.

The next day, pressure in the central retinal arteries measured 30 mm. Hg diastolic on the right and 70 mm. diastolic on the left, which suggested occlusion of the proximal portion of the right carotid artery. The patient died. Necropsy revealed infarction of the right frontoparietal region and thrombosis of the right carotid artery 2 cm. distal to the site of operation. Both carotid arteries showed marked atherosclerotic changes.

**Case 3.** A 62-year-old man was examined at the Mayo Clinic on August 8, 1959, because he had had a febrile illness for two weeks. When examined, his symptoms had subsided somewhat.

On August 11, the patient was examined by an internist who palpated the right carotid artery lightly. During palpation, the cardiac rate or rhythm was not altered but weakness of the left side of the body developed immediately. When a neurologist examined the patient five minutes later, he found complete paralysis of the left upper limb and the left side of the face. The left lower limb was slightly weakened, with extensor response to plantar stimulation on that side. He had complete left homonymous hemianopsia, and the diastolic pressure in the central retinal artery was 100 mm. Hg in each eye.

Laboratory findings were urine, normal; blood hemoglobin, 13 gm.; leukocyte count, 5,500, with differential smear showing normal proportion of cell types; erythrocyte sedimentation rate (Westergren method), 46 mm. in one hour; and serologic reaction for syphilis, negative.

Roentgenographic examination of the head, thorax, esophagus, stomach, and duodenum gave normal results. Cholelithiasis was demonstrated radiographically.

The patient was dismissed from the hospital on August 25, with some improvement in his weakness. While he was hospitalized, he recalled that, in the week before examination, he had had 3 or 4 attacks of weakness on the left side of his body, each lasting twenty to thirty minutes.

**Case 4.** A 66-year-old man who had an epithelioma of the right tonsillar region and a metastatic nodule in the right submaxillary region had received roentgen therapy in another community in January 1956. He came to the Mayo Clinic in July 1956, and a block dissection of the cervical lymph nodes on the right was carried out. No evidence of metastatic disease was found.

On January 21, 1957, he returned to the Mayo Clinic for reexamination. The examiner was gently palpating in the region of the right carotid artery for lymph nodes when the patient suddenly became unable to follow directions. His head and eyes deviated to the right, and his left arm was flaccid. Ten minutes later, a neurologist detected complete flaccid paralysis of the limbs of the left side and an extensor response to plantar stimulation on that side. Although the patient was alert, oriented, and coherent, he seemed unaware of the left side of his body and was unable to identify body parts on that side. The diagnosis of occlusion of a branch of the middle cerebral artery on the right with involvement of the parietal lobe was made, and the patient was hospitalized.

One hour after the initial observation, the patient was again examined and his blood pressure was found to be 170/90. He was oriented and did not complain of pain. When asked to move the left upper or lower extremities, he would instead move the corresponding limbs on the right and would add that he could not find the left arm or leg. The head and eyes continued to deviate to the right, and complete left homonymous hemianopsia was present.

On January 26, the patient was able to move his eyes to the left and retinal arterial pressure was 40 mm. diastolic in each eye.

By February 4, the patient was able to walk. He had moderate weakness of his entire left upper limb, with the most severe weakness being in the left biceps muscle. He was unable to calculate well or to readily identify fingers of his left hand and exhibited marked apraxia when he attempted to dress himself. He left the hospital on that date.

Laboratory findings were urine, normal; blood hemoglobin, 12.7 gm.; leukocyte count, 9,300; and serologic reaction for syphilis, negative.

Roentgenographic examination of the head gave normal results. Electrocardiographic findings also were normal.

The patient returned on October 28, 1957. He continued to demonstrate faulty identification of fingers of his left hand. He had difficulty calculating and some difficulty dressing himself. Slight weakness of his left upper extremity was noted. The left biceps reflex was slightly hyperactive, but the previously positive Babinski sign had disappeared. Recurrence of the epithelioma was detected in the right tonsillar region.

The patient was seen again in July 1958. His neurologic status had changed little. Further growth of the epithelioma was noted, but further treatment was not deemed possible.

It was subsequently learned that the patient underwent radical surgical removal of part of the right mandible and soft palate in another community early in 1959. At the time of operation, it was necessary to ligate the right internal carotid artery. This was followed by left hemiplegia which persisted until death of the patient in June 1959.

## COMMENT

We have shown that various types of manipulation of the carotid arteries can be associated with clinical cerebral infarction and that even gentle pressure over the carotid artery is not without danger. Each of the patients we have described was subjected to manipulation in the region of the carotid for a different reason, but in all the results were similar.

The possible mechanisms that produce the neurologic complications we have described include [1] bradycardia and hypotension associated with stenosis of a specific artery, [2] manual compressive occlusion without or with change in blood pressure, [3] reflex vasospasm, [4] embolization from local atheroma, and [5] local trauma to the carotid artery with subsequent thrombosis or dissecting aneurysm.

In each of the patients we have described and in all of those reported on by Askey,[5] the cerebral lesion was on the same side as the vessel that was manipulated. It seems very unlikely that systemic hypotension or bradycardia, which would produce decreased blood flow to both sides of the brain, would by chance affect the "correct" side in every patient. Marmor and Sapirstein[4] felt that hypotension and bradycardia may have been

contributory factors in the thrombosis of the anterior cerebral arteries in their patient. The patient apparently recovered completely from the initial syncope and was normal for several minutes before he again became unresponsive. This period of normality suggests that bradycardia or hypotension was not the direct cause of the thrombosis. Askey has supplied additional documentation for our suggestion; in 2 of his patients, cerebral infarction occurred without change in heart rate or blood pressure.

Occlusion or stenosis of the carotid artery by manual compression may have been responsible for some of the complications we have described. The young man in our series who manifested contralateral weakness during the time firm pressure was applied to his neck probably did so because the carotid artery was occluded. In 2 cases reported by Askey, hemiplegia probably developed because of the same mechanism. In 3 of our patients, the examiner thought that sufficient pressure was never brought to bear to occlude the vessel. The course of patients who are asymptomatic for several minutes after release of carotid pressure and then manifest neurologic defects suggests that occlusion of the vessel by manual compression is not the cause of the defects. Patients who have had spontaneous transient episodes of neurologic deficit attributable to insufficiency of the carotid-artery system may suffer irreversible cerebral damage if the blood flow in the carotid artery is further reduced by even gentle pressure over the vessel. This may occur in patients with marked stenosis of the carotid arteries who have not had intermittent symptoms before manipulation of their neck. In all these patients, systemic blood pressure may or may not drop during the time the carotid artery is occluded.

Disagreement exists about the occurrence of narrowing of the lumen of cerebral blood vessels as a reflex response to stimulation of the carotid sinus. Engel[10] found electroencephalographic changes in the ipsilateral cerebrum in 2 patients after massage of the carotid sinus. Neither of these patients exhibited abnormalities when attempts were made to occlude the common carotid artery by digital compression below the bifurcation. Gurdjian and associates[11] detected syncope without alteration in pulse or blood pressure in 63 of 100 patients with hemiplegia or hemiparesis when the carotid artery on the side opposite the cerebral lesion was compressed. They felt that the symptoms were the result of occlusive disease in the vessels opposite the side compressed rather than cerebral vasoconstriction from stimulation of the carotid sinus.

Some of the authors who have previously reported irreversible neurologic changes as a result of carotid manipulation have attributed these changes to this cerebral reflex type of carotid-sinus irritability. While it is possible that in several of the patients described here and elsewhere cerebral infarction developed as a result of vasospasm, there are several arguments against this. Most of the patients described have been more than 60 years old. Those who have died had significant atherosclerosis of the cerebral vessels. It seems unlikely that these vessels, which have extensive change associated with aging, have the ability to constrict in response to any type of stimulus.

Manipulation of any sclerotic vessel may cause atheromatous material from the wall of the vessel to be dislodged and to move distally. When this occurs in the carotid artery, irreversible cerebral damage may abruptly occur. We believe that embolism may explain the sudden onset of hemiparesis after relatively gentle carotid manipulation. From correlation of clinical patterns and necropsy findings, it is known that cerebral infarction manifested by an almost instantaneous onset of the maximal neurologic deficit usually is caused by embolism. Vasospasm has never been proved to play a significant role in the pathogenesis of such infarction. Therefore, if carotid manipulation is accompanied by the instantaneous onset of maximal degree of neurologic deficit, it appears unlikely that spasm is responsible.

Local trauma to the carotid artery during manipulation is not to be discounted as a cause of complications of this procedure. Trauma to carotid arteries that have narrowing and intimal changes as a result of atherosclerosis may produce further damage to the intima with resultant thrombus formation and occlusion. This process might occur several minutes after cessation of any manipulation.

Local trauma to the carotid artery may also produce bleeding into the wall of the vessel, with formation of a dissecting aneurysm. As this process progresses, the lumen of the vessel may be occluded and cerebral infarction may occur. It would be expected that the neurologic manifestations of such an aneurysm would occur some hours after carotid manipulation. It is likely that, in several of the cases reported by other authors, carotid occlusion developed on the basis of these mechanisms.

The exact cause of the cerebral infarction suffered by each of the patients we have described is not precisely known. Patient 1 was likely subjected to manual occlusion of the carotid artery with resultant cerebral ischemia sufficient to produce infarction. Patient 2 underwent a surgical procedure. Great care was exercised to prevent occlusion of the carotid artery, but local trauma may have produced thrombosis.

Several possible explanations exist for the catastrophic complications suffered by patients 3 and 4. Neither of these patients experienced syncope, and patient 3 was observed to have no alteration in heart rate. In each, onset of the neurologic defect was immediate. This type of onset is characteristic of cerebral embolism. It seems possible that such an embolus could result from the dislodging of atheromatous material from the wall of the carotid artery. However, an alternate explanation is that the carotid arteries of each of these patients were markedly narrowed by atherosclerosis and that gentle palpation was sufficient to further reduce the blood supply distally and cause infarction. Because of the temporal relationships and the arguments previously presented, the case for vasospasm as the mechanism responsible for infarction in these patients is tenuous.

SUMMARY

Palpation, massage, and compression of the carotid arteries in the neck are commonly considered to be innocuous procedures. Detailed reports on 4 patients are given to document the fact that such carotid manipulation occasionally produces serious focal cerebral damage.

The possible mechanisms of production of these complications have been discussed. It appears probable that decrease in systemic blood pressure, bradycardia, and cerebral vasospasm are not the direct causes of the complications. It is suggested that cerebral infarction may be produced by manual occlusion of the artery, by embolization of dislodged atheromatous material, and by local trauma to the vessel with subsequent carotid thrombosis or formation of a dissecting aneurysm.

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# Cerebrovascular effects of topically applied serotonin in the cat

R. B. Raynor, M.D., J. G. McMurtry, M.D.,
and J. L. Pool, M.D.

SUBSTANTIAL EVIDENCE now exists indicating that cerebral vasospasm frequently occurs after rupture of an intracranial aneurysm.[1] Serious complications, such as local or remote areas of cerebral softening, infarction, or massive cerebral edema, apparently may be caused in some cases by severe vasospasm. Since this type of vasospasm is so often associated with subarachnoid hemorrhage after rupture of an intracranial aneurysm and tends to disappear as extravasated blood is absorbed, it was thought that some substance in the blood might be a causative factor. Serotonin (5-hydroxytryptamine) was selected for study because it is present in platelets and is known to have a marked constrictor action on peripheral arteries.[2] Experiments were therefore conducted to determine whether serotonin exerted similar effects on cerebral arteries.

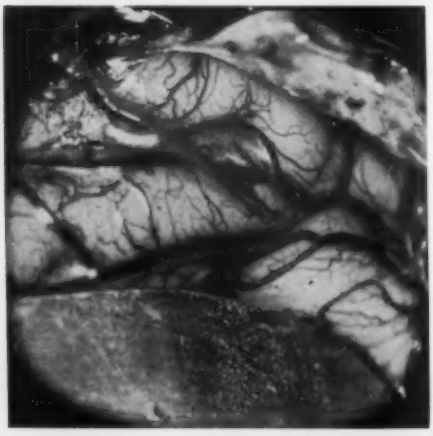

Fig. 1. Normal branches of middle cerebral artery of cat

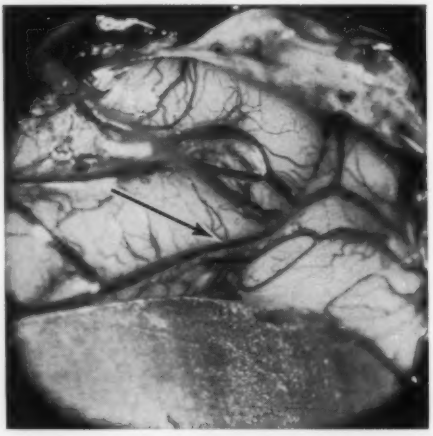

Fig. 2. Arteries in Figure 1 twelve minutes after 0.05 cc. of serotonin creatinine sulfate has been applied. Arterial diameter has decreased 33%. Arrow points to region of maximal effect.

## EXPERIMENTAL METHOD

In 27 cats, the middle cerebral arteries were exposed by craniotomy and the animals so prepared that the widths of these vessels could be photographed at appropriate intervals through a Zeiss operating room microscope with a robot camera attachment. Color pictures were later projected so that the vessels could be carefully measured. The entire method is described in a previous report.[3]

A 1½-in. No. 25 hypodermic needle was mounted on a 3-coordinator manipulator so

From the Department of Neurological Surgery, College of Physicians and Surgeons, Columbia University, and the Neurological Institute, Presbyterian Hospital, New York City.

that its point was a few millimeters above a branch of the middle cerebral artery.

At thirty-second intervals, 3 or more control pictures were taken. Then, 0.05 cc. of serotonin (serotonin creatinine sulfate) in a concentration of 1:1,000 or 1:100,000, buffered to a *p*H of 7.3 solution, was applied by dripping it onto the vessel and adjacent brain through the No. 25 needle. (Previous experiments had shown that dripping isotonic saline on the vessels had no effect. Therefore, the mechanical factor was felt to be unimportant, and no further studies were undertaken.) Pictures were taken at thirty-second intervals for five minutes and then at three-minute intervals for thirty minutes to three hours. The serotonin application was repeated at least once on the same vessel in every experiment.

Blood from 6 cats was tested for vasoconstrictor properties. In 2 animals, studies were conducted with serum obtained from blood allowed to clot one to three days in the refrigerator. The specimens were then centrifuged, and the serum was decanted and applied to the arteries by the method described above. In 4 other animals, fresh venous blood was drawn from the animals and immediately applied to the vessels. This was repeated 2 to 4 times, and the vessels were observed in the usual manner. In 3 of these animals, a specimen drawn at the start of the experiment was allowed to clot for thirty minutes and then centrifuged and the serum was decanted. After observations with fresh blood had been completed, 0.05 cc. of this serum was applied to the same vessel 2 to 4 times.

Finally, xanthochromic spinal fluid from 3 patients who had had subarachnoid hemorrhage three to seven days previously was applied to the vessels of 3 animals. In these animals, subsequent observations were also made after application of serotonin or stored serum.

Fig. 3. Normal cortex and middle cerebral artery branches of cat. Numerous fine arterioles can be seen.

Fig. 4. Arteries and adjacent cortex (Fig. 3) five minutes after 0.05 cc. of serotonin creatinine sulfate was applied through No. 25 hypodermic needle seen in photograph. Major arteries are constricted and caliber and number of visible arterioles have decreased. Cortex appears blanched because of its decreased vascularity.

## RESULTS

Application of serotonin to an artery resulted in marked spasm for a distance of 1 to 2 cm. from the point of application in every instance. The vessels contracted 20 to 40% of their original size for varying periods of time (Figs. 1 and 2).

In some preparations, marked cortical

TABLE 1

RESULTS OF SEROTONIN APPLICATION TO CORTICAL VESSELS

| *Animal no.* | *Serotonin concentration (gm. per liter of serotonin creatinine sulfate)* | *Duration of spasm min. (minutes)** | *Comment* |
|---|---|---|---|
| 1 | 1/1,000 | 2 | |
| | | 33+† | |
| | | 17+ | |
| 2 | 1/1,000 | 35+ | Cortex blanched for 2 minutes after serotonin application by visual observation‡ |
| | | 24+ | |
| 3 | 1/1,000 | 10+ | Cortex blanched for several minutes (visual observation) |
| 4 | 1/1,000 | 120+ | |
| 5 | 1/1,000 | 96 | |
| | | 5+ | |
| 6 | 1/1,000 | 10+ | Cortex blanched |
| 7 | 1/1,000 | 130 | |
| | | 54+ | |
| 8 | 1/1,000 | 165 | Xanthochromic spinal fluid from patient with subarachnoid hemorrhage previously applied had no effect on same vessel |
| 9 | 1/1,000 | 180 | Spinal fluid from patient with subarachnoid hemorrhage first applied to vessel without any effect |
| 10 | 1/50,000 | 30 | |
| 11 | 1/100,000 | 9 | |
| 12 | 1/100,000 | 35 | |
| | | 30 | |
| | | 23+ | |
| 13 | 1/100,000 | 34+ | |
| 14 | 1/100,000 | 14 | 11 to 14 minutes after serotonin application, artery got larger than its original size. It then returned to its original size. |
| | | 10 | |
| | | 9 | |
| 15 | 1/100,000 | 45 | |
| | | 42+ | |
| | | 39+ | |
| 16 | 1/100.000 | 83 | |
| | | 78 | |
| | | 32 | |
| 17 | 1/100,000 | 120 | |
| | | 120 | |
| | | 30 | |
| 18 | 1/100,000 | 21 | |
| | | 2 | |
| 19 | 1/100,000 | 9 | |
| | | 21 | |
| | | 5 | |
| 20 | 1/100,000 | 12 | |
| | | 90 | |
| | | 30 | |
| 21 | 1/100,000 | 120 | |
| | | 70 | |

*Multiple times listed for any animal refer to repeated application of serotonin.

†Plus sign after time indicates that vessel size was not recorded for a long enough period of time to accurately determine when it returned to its original size.

‡Though cortical blanching was very obvious visually, it did not record well enough on film to be reproduced.

blanching was also observed in the area of serotonin application (Figs. 3 and 4). On 4 occasions, this was visible to the naked eye and lasted one to ten minutes, covering an area of 1 to 2 cm. around the point of serotonin application. This transient ischemia of the cortex was always of shorter duration than the vasoconstriction of the larger vessels.

Initially, when a concentration of 1:1,000 of serotonin was used, resulting vasospasm lasted at least two hours and ten minutes, while, in some animals observed for three hours, an end point was never established.

In an effort to establish an end point for the duration of the spasm, serotonin in a concentration of 1:100,000 was used in 12 animals. Spasm lasted nine minutes to two hours or more, as indicated in Table 1.

All applications of serum from blood that had been allowed to clot caused vasospasm comparable to that due to serotonin application (Figs. 5 and 6). However, when freshly drawn blood was immediately applied to the observed vessels, no spasm was detected (Table 2).

In the trial of xanthochromic cerebrospinal fluid obtained from 3 patients three to seven days after subarachnoid hemorrhage, no spasm was observed in any of the 3 animals tested. However, serotonin or serum applied a short time later to the same vessels always produced spasm of these vessels (Table 3).

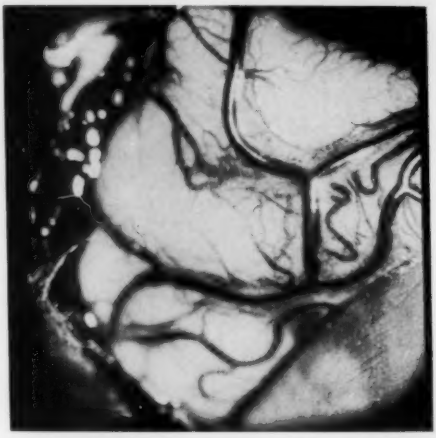

Fig. 5. Normal branches of middle cerebral artery of cat

Fig. 6. Artery in Figure 5 twelve minutes after 0.05 cc. of serum was applied to vessel and adjacent cortex. Blood was allowed to clot for thirty minutes before serum was removed. Arrow points to area of maximal effect. Arterial diameter has been reduced 30%.

## DISCUSSION

The presence of a vasospastic factor in the blood has been postulated for many years. Ludwig and Schmidt[4] mentioned such a substance in 1868 when they met unexpected resistance while trying to perfuse dog muscle with defibrinated blood. Later, investigators localized this substance in the platelets when it was noted that a vasoconstrictor substance was liberated into the serum during blood clotting. It was shown that this substance was not histamine.[5,6] If the platelets were carefully removed from the serum first, no vasoconstrictor effect was observed.[7] Rapport, Green, and Page[8] isolated this vasoconstrictor substance, which they called serotonin, in its crystalline form as serotonin creatinine sulfate. Their original source was beef serum. Rapport[9] later identified the active constrictor agent of serotonin as 5-hydroxytryptamine. Though most investigators doubt the existence of other constrictor agents in the blood,[10] some controversial evidence was presented by Humphrey and Jaques,[11] who found 5% of constrictor effect still remained in platelet extract

TABLE 2
FRESH WHOLE BLOOD AND SERUM APPLICATIONS TO VESSELS

| Animal no. | Substance applied to vessel | Number of applications | Results of application: Spasm | Results of application: No spasm |
|---|---|---|---|---|
| 22 | Serum from blood that had been refrigerated 3 days | 2 | x<br>x | |
| 23 | Serum from blood allowed to clot one hour, then centrifuged serum removed and refrigerated overnight | 2 | x<br>x | |
| 24 | Freshly drawn blood* | 2 | | x<br>x |
| | Serum from blood allowed to clot 30 minutes | 2 | x<br>x | |
| 25 | Freshly drawn blood* | 2 | | x<br>x |
| | Serum from blood allowed to clot 30 minutes | 2 | x<br>x | |
| 26 | Freshly drawn blood* | 4 | | x<br>x<br>x<br>x |
| | Serum from blood allowed to clot 30 minutes | 4 | x<br>x<br>x<br>x | |
| 27 | Freshly drawn blood* | 3 | | x<br>x<br>x |

*A fresh specimen of blood was drawn for each application.

when serotonin and histamine were inhibited. Moussatché[12] has also presented evidence of another platelet factor.

After blood vessels have been cut, they normally contract. Zucker[13] investigated the interrelationship of this phenomenon and serotonin using rat mesenteric vessels and concluded that the cut vessel contracted locally from the mechanical stimulus but that adjacent vessels contracted only when a platelet plug was present in the cut vessel. The constriction of the adjacent vessels was attributed to serotonin released from the disrupted platelets. Zucker and Borrelli[14] have also shown that about half of the platelet serotonin is released rapidly during normal coagulation. The remainder becomes available during the next several days. This phenomenon may account for the prolonged nature of cerebral vasospasm.

TABLE 3
SUMMARY OF RESULTS

| Substance applied to vessels | Number of experiments | Results: Vascular spasm | Results: No effect |
|---|---|---|---|
| Serotonin | 21 | x | |
| Serum from coagulated blood | 5 | x | |
| Freshly drawn blood | 4 | | x |
| Cerebrospinal fluid from patients with subarachnoid hemorrhage | 3 | | x |

Hardisty and Stacey[15] have found that the serotonin content of whole human blood is 0.16 μg. per cubic centimeter. In most of our experiments, 0.05 cc. of serotonin creatinine sulfate diluted to 1:100,000 was used. Since serotonin creatinine sulfate contains 43.25% serotonin, the concentration used in these ex-

periments thus amounted to 2.16 μg. of serotonin. It would require 13.5 cc. of whole human blood to provide this amount of serotonin, and this seems a reasonable estimate of the amount of blood that may leak from a ruptured aneurysm.

It is possible therefore that serotonin from extravasated blood may cause or contribute to localized vasoconstriction.

Angiographically demonstrated spasm may affect vessels close to a recently ruptured aneurysm and, in some cases, may extend for some distance but seldom involves the entire cerebral circulation. A reasonable explanation of these observations, suggested by the present work, is that only those vessels close enough to be bathed by a critical concentration of serotonin will exhibit constriction. The relatively large quantity of spinal fluid may so dilute the serotonin that distal vessels may not be exposed to sufficient concentration to cause vasospasm. Moreover, it has been reported that the experimental introduction of blood into the subarachnoid space of animals failed to cause vasospasm.[16] The dilution factor may also explain this.

Of additional interest was the cortical blanching that occurred for five to ten minutes. In an area of brain already subject to prolonged decreased blood flow from its major vessels by virtue of vasospasm, this further insult may be all that is necessary to destroy viability.

No obvious explanation is available at present for the marked variability in the duration of spasm. Possibly, varying degrees of operative retraction of the brain may have played a role, but in all probability the explanation is complex.

## SUMMARY AND CONCLUSIONS

1. The problem of neurologic symptoms in subarachnoid hemorrhage is discussed. Cerebral vasospasm is presented as one of the etiologic mechanisms of these symptoms.

2. Serotonin (5-hydroxytryptamine) is an active vasoconstrictor substance present in blood platelets and is apparently released whenever platelets are disrupted during clotting.

3. Serotonin was applied topically to major cerebral arteries and the cortex of cats. Prolonged localized spasm of these arteries was observed. Marked blanching of the treated cortex was also seen.

4. Small quantities of serum from clotted blood caused vasospasm comparable to that caused by serotonin. Fresh blood did not cause vasospasm.

5. While undoubtedly there are other mechanical, neurogenic, and possibly chemical factors, it is postulated that serotonin liberated from the platelets of extravasated blood may play a significant role in the pathogenesis of cerebral vasospasm following rupture of an intracranial aneurysm.

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# Possible mechanisms of action of hypertonic urea in reducing intracranial pressure

Thomas W. Langfitt, M.D.

In 1919, Weed and McKibben[1] demonstrated that intravenous administration of hypertonic solutions reduced intracranial pressure. In their initial experiments, they used various concentrations of sodium salts and hypertonic glucose. For several years after these observations were published, numerous studies were carried out in experimental animals and in patients with intracranial lesions. A marked decrease in pressure was reported with hypertonic saline[2–4] and glucose.[5–8] Dowman[9] and Fay[10,11] introduced magnesium sulfate for this purpose and believed that it was more effective than hypertonic saline.

However, in 1930, Browder[12] described several patients with head injuries in whom 50% glucose produced a significant and prolonged elevation of cerebrospinal fluid pressure. Subsequently, several investigators demonstrated that both hypertonic glucose and hypertonic saline frequently produced a secondary rise in cerebrospinal fluid pressure, often of considerable magnitude.[13–16] Interest in magnesium sulfate waned when it was shown that large doses of the drug occasionally produced hypovolemic shock. Since magnesium sulfate was administered orally or per rectum and was retained in the intestinal tract, it resulted in decreased blood volume in addition to the reduction in intracranial pressure.

The mechanism of action of these substances was assumed to be the induced increase in osmotic pressure of the blood. This resulted in transport of water from the brain and cerebrospinal fluid to the blood and a concomitant fall in intracranial pressure. The agents which caused a secondary rise in pressure presumably did so because they crossed the cell membrane. As the concentration in blood and the extracellular fluid of the brain fell, the osmotic gradient was reversed and fluid entered the cell, resulting in intracellular edema. Foley and Putnam[3] provided some experimental evidence for this hypothesis by demonstrating that administration of water to animals produced a greater increase in cerebrospinal fluid pressure if the animals had been given hypertonic saline several hours previously.

Interest was then directed to compounds with large molecular weights which penetrated the blood-brain and blood–cerebrospinal fluid barriers very slowly. Masserman[17] gave 50% sucrose to 35 patients, none of whom had intracranial pathology. He observed a mean fall in cerebrospinal fluid pressure of 95 mm. of water without undesirable clinical effects. However, Jackson, Dickerson, and Gunther[18] gave hypertonic sucrose to 8 patients with severe head trauma, and, in 2 cases, there was a definite secondary rise in cerebrospinal fluid pressure. Also, in 3 cases, there was no apparent response to the sucrose. Sodium arabinate, a salt of arabinic acid which is obtained from gum arabic, was investigated by Hughes and Laplace.[19] Reduction in cerebrospinal fluid pressure was less rapid than with 50% glucose, but the effect was maintained over a longer period of time and a secondary increase in pressure was not mentioned. However, preparation of the substance was expensive.

None of these compounds appeared to have any specific toxic effect until Helmholz[20] described pathologic changes in the kidneys of rabbits after hypertonic sucrose. Several years later, Anderson and Bethea[21] demonstrated alterations in the cells of the renal convoluted tubules of 6 patients who had received this agent, and Lindberg, Wald, and Barker[22]

From the Division of Neurological Surgery, The Johns Hopkins University, Baltimore.

described similar lesions in dogs. Although definite evidence was lacking for an associated impairment of renal function, these findings were considered to be unequivocal evidence of a nephrotoxic effect.

In the course of investigating the effects of various solutions on intraocular and intracranial pressure, Fremont-Smith and Forbes[23] used 50% urea, 30% sodium chloride, and 50% glucose. On the basis of the illustrations in their paper, there appeared to be no significant difference in the ability of these agents to reduce intracranial pressure. However, in this and subsequent papers,[24,25] their primary interest was in problems other than the comparative effects of these solutions.

There appear to have been few investigations in this field between 1940 and 1950, when interest in urea was revived by the experiments of Smythe, Smythe, and Settlage.[26] In monkeys, they found that 50% urea produced a fall in cerebrospinal fluid pressure fourfold the effect of either 50% glucose or 50% sucrose. Since then, Javid and Settlage[27,28] and more recently Katz[29] and Taheri[30] have described the effectiveness of urea in reducing intracranial pressure in human beings with a variety of brain lesions.

The purposes of the present investigation were to assess the variability in individual response to urea and, by correlating the changes in intracranial pressure with alterations in the chemical composition of the blood and cerebrospinal fluid, to attempt to learn more of its mechanism of action. On theoretic grounds, urea should not be as effective an osmotic agent as sucrose since, with a smaller molecular weight, urea should penetrate the blood-brain and blood–cerebrospinal fluid barriers more rapidly. In addition, because urea crosses the cell membrane, it possesses the same theoretic disadvantage, a secondary increase in intracranial pressure, which was the principal criticism of hypertonic glucose. Another purpose of this investigation was to study the effect of urea in patients with pseudotumor cerebri. This will be the subject of a subsequent report.

## METHOD

Data for this report were obtained from 10 patients. The cerebrospinal fluid pressure was measured in 8 patients. A lumbar puncture needle was inserted in the lumbar subarachnoid space and was attached to a standard water manometer supported by a stand. In addition, a U-shaped manometer attached to the standard manometer by a 3-way stopcock was used to measure subatmospheric pressures. Pressures were recorded at intervals of one to ten minutes, depending on the degree of fluctuation of the column of fluid. A thirty-minute control period preceded the administration of urea in each patient; the cerebrospinal fluid pressure was then observed for six to fourteen hours after the urea infusion. In 5 patients, twenty-four-hour pressure levels were determined, and, in 2 patients, daily pressure measurements were obtained for several days.

Lyophilized urea (Urevert or Ureaphil) was used as a 25 to 30% solution in 5% dextrose and water or 10% invert sugar and administered intravenously. The dose range was 0.5 to 1.5 gm. per kilogram. The rate of infusion was about the same in all patients, and the maximum infusion time was thirty minutes.

Numerous chemical analyses of the serum, cerebrospinal fluid, and urine were carried out. Control samples of serum and cerebrospinal fluid were drawn, then additional samples were obtained at thirty minutes, one hour, and, with rare exceptions, at hourly intervals after the beginning of the urea infusion, for as long as the cerebrospinal fluid pressure was observed. Urine volume and urea excretion were determined in several patients before and at frequent intervals after urea administration.

The serum and cerebrospinal fluid studies included urea nitrogen, sodium, potassium, chloride, and osmolality. Urea levels were determined by Archibald's modification of the Ormsby method, using the Technicon autoanalyzer. Sodium and potassium levels were measured by flame photometry and chlorides by the Cotlove chloride-meter. The freezing point depression technic employing the Bowman osmometer was used to determine osmolalities.

Each patient was given fluids to approximate the urine output. The fluids were 5% dextrose in water intravenously or by nasogastric tube and tap water for the 2 patients who were able to take fluids orally.

RESULTS

**Cerebrospinal fluid pressure.** In all patients, urea produced a marked depression of cerebrospinal fluid pressure, maximum reduction occuring between fifty-five and ninety minutes after the beginning of the infusion. Although the initial response to intravenous urea was rather uniform, the subsequent pressure effects were quite variable. The time required for return of pressure to control values varied between two and six and one-half hours in 6 patients, and, in 2 patients, the pressure remained below control values throughout the period of observation, twenty-four hours and six days, respectively.

Table 1 shows that there is not a dose-effect correlation unless the initial pressure is taken into consideration. Then there is a suggestion that the greater the initial cerebrospinal fluid pressure, the greater is the reduction in pressure with urea. This is particularly apparent in the last column of the table, in which the assumption is made that the fall in pressure is proportional to the dose and estimates are made of the reduction in pressure the patients would have had if all had received 1 gm. per kilogram.

Of the 2 patients with prolonged reduction of cerebrospinal fluid pressure, 1 (R. H., Fig. 1) had a bronchogenic carcinoma with metastasis and was virtually moribund at the time of the study. The second patient (A. A., Fig. 1) had a diagnosis of pseudotumor cerebri. Patients W. D. and B. H. (Fig. 2) had gradual return of pressure to the original level.

Of particular interest are the 4 patients whose cerebrospinal fluid pressure exceeded the control pressure during recovery from the initial urea effect. In 3, the maximum secondary rise was 100 mm., but, in the fourth, it was 250 mm. of water; 3 of the patients received additional infusions of urea, and in each instance there was again a marked fall in pressure. However, in all 3, the pressure ultimately stabilized at the level of the secondary elevation. Thus, Figures 3 and 4 demonstrate that repeated administrations of urea continue to be effective in reducing intracranial pressure but the magnitude of the response is not always proportional to the dose administered; also, if a secondary increase in intracranial pressure occurs after the initial infusion of urea, it will occur again after repeated doses.

**Blood and cerebrospinal fluid chemistries.** In Tables 2 and 3 are presented the serum urea nitrogen values for 10 patients before administration of urea and at frequent intervals thereafter; 1 patient had a markedly elevated control value, and the values in 3 others were minimally elevated. All of the patients showed a rapid elevation in serum urea nitrogen after the urea infusion, with the maximum level attained at thirty minutes except for 1 individual (J. W.). However, in none of these patients did the maximum re-

TABLE 1
DOSE–EFFECT RESPONSE OF CEREBROSPINAL FLUID PRESSURE

| *Patient* | *Dose of urea (gm. per kg.)* | *Initial pressure (mm. $H_2O$)* | *Maximum pressure reduction (mm. $H_2O$)* | *Estimated pressure reduction with 1 gm. per kg. (mm. $H_2O$)* |
|---|---|---|---|---|
| W.D. | 1.2 | 145 | 140 | 116 |
| R.H. | 1.4 | 120 | 160 | 115 |
| G.F. | 1.0 | 140 | 145 | 145 |
| B.H. | 1.0 | 200 | 150 | 150 |
| J.W. | 1.5 | 125 | 225 | 150 |
| E.H. | 1.2 | 220 | 280 | 233 |
| R.B. | 0.5 | 300 | 185 | 370 |
| A.A. | 0.7 | 360 | 280 | 410 |

In Figures 1 through 4, cerebrospinal fluid pressure in millimeters of water (ordinate) is plotted against time (abscissa). Pressures were recorded at one- to ten-minute intervals, and each point on the charts is the average pressure for either fifteen or thirty minutes, as noted. A solid line indicates periods of continuous recording and broken lines, periods when pressure was not recorded. All urea infusions were begun at time 0 with subsequent infusions indicated by arrows. See Tables 2 and 3 for dosage.

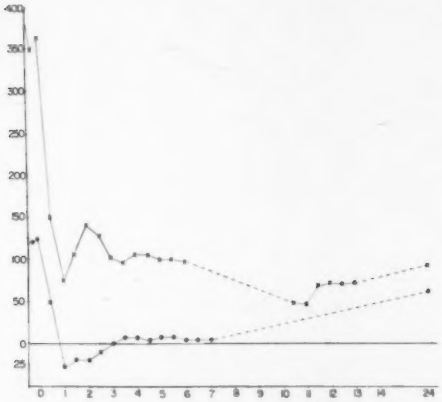

Fig. 1. A.A. (x-x), a patient with pseudotumor cerebri, had daily cerebrospinal fluid pressure recordings for six days after this single dose of urea and at no time did pressure exceed 150 mm. of water after the initial fall. R.H. (·—·) was virtually moribund and died forty-eight hours after the beginning of the study.

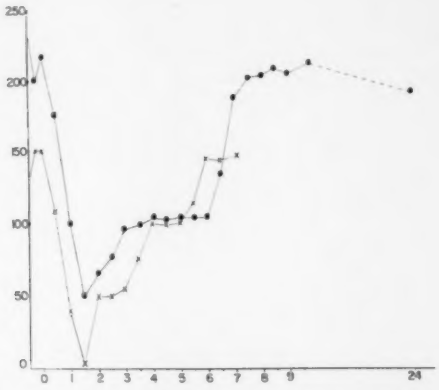

Fig. 2. Patients B. H. (·—·) and W. D. (x-x) had a moderate reduction in cerebrospinal fluid pressure with a gradual return to control levels.

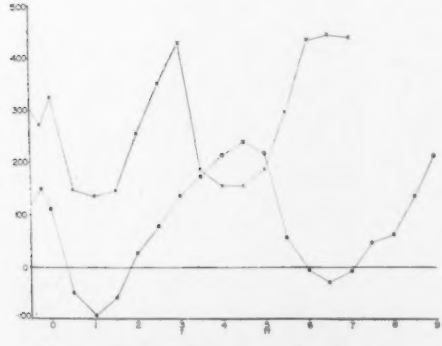

Fig. 3. Both R. B. (x-x) and J. W. (·—·) showed a significant secondary rise in cerebrospinal fluid pressure after the initial urea effect. In both patients, pressure fell promptly with a second dose of urea (R. B., single arrow; J. W., double arrow) but ultimately returned to the level of the secondary elevation.

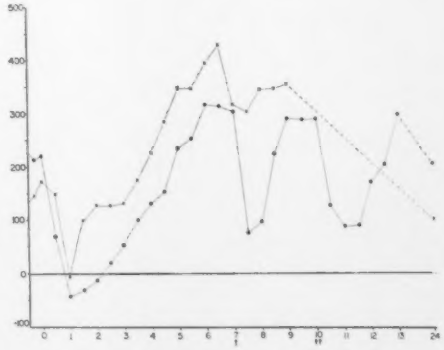

Fig. 4. Both G. F. (x-x) and E. H. (·—·) had secondary elevation in cerebrospinal fluid pressure after initial urea effect. Degree of secondary elevation in G. F. was the most marked observed in this study. E. H. received multiple doses of urea (single arrow, second infusion; double arrow, third infusion) and each time pressure fell promptly. However, pressure ultimately returned to level of secondary elevation. In both patients, cerebrospinal fluid pressures approximated control values at twenty-four hours.

TABLE 2

SERUM UREA NITROGEN (MILLIGRAMS PER CENT)

| Patient | Dose | Control | Time (hours) after beginning of urea infusion: ½ | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 7½ | 8 | 9 | 10 | 10½ | 11 | 12 | 24 | 48 | 96 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| F.B. | 80 gm. (1.4 gm. per kg.) | 9 | 150 | 134 | 105 | | | | 87 | | | | | | | | 74 | | | |
| G.F. | 80 gm. (1 gm. per kg.) | 13 | 97 | 91 | 81 | 78 | 68 | 57 | 53 | 47 | | 45 | 41 | | | | | 25 | 29 | 23 |
| E.K. | 40 gm. (0.6 gm. per kg.) | 82 | 115 | 94 | 94 | 88 | | | | | | | | | | | 43 | 150 | | |
| E.H. | * | 24 | 139 | 125 | 103 | 89 | 79 | 72 | | 55 | 106 | 100 | | 87 | 142 | 123 | | 53 | 17 | 12 |
| B.H. | 80 gm. (1 gm. per kg.) | 14 | 120 | 102 | 83 | 76 | 67 | | 56 | | | 44 | | | | | | 28 | | |

*Initial dose, 80 gm. (1.2 gm. per kilogram), followed by 40 gm. (0.6 gm. per kilogram) at seven hours and 40 gm. at ten hours

TABLE 3

SERUM AND CEREBROSPINAL FLUID UREA NITROGEN (MILLIGRAMS PER CENT)

| Patient | Dose of urea | | Control | Time (hours) after beginning of urea infusion: ½ | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 7½ | 8 | 9 | 10 | 10½ | 11 | 12 | 13 | 24 | 36 | 48 | 72 | 96 | 120 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| W.D. | 80 gm. (1.2 gm. per kg.) | Serum | 5 | 262 | 105 | 90 | 85 | 74 | 65 | 33 | 50 | | | | | | | | | | | | | | |
| | | Fluid | 6 | 13 | 30 | 40 | 44 | 43 | 42 | 47 | 46 | | | | | | | | | | | | | | |
| R.H. | 80 gm. (1.4 gm. per kg.) | Serum | 18 | 120 | 116 | 100 | 96 | 84 | 84 | 79 | | | | | | | | 69 | | | 81 | | | | |
| | | Fluid | 18 | 19 | 23 | 30 | 38 | 45 | 50 | 57 | | | | | | | | 43 | | | 70 | | | | |
| J.W. | * | Serum | 21 | 129 | 140 | 132 | 121 | 107 | 98 | | 90 | 129 | 125 | 117 | 106 | | 96 | | | | | | | | |
| | | Fluid | 21 | 42 | 71 | 114 | 117 | 107 | 100 | | 92 | 98 | 106 | 114 | 110 | | 103 | | | | | | | | |
| A.A. | 40 gm. (0.7 gm. per kg.) | Serum | 8 | 97 | 78 | 65 | 55 | 51 | 45 | 40 | | | | | | | 28 | 26 | 24 | 15 | | 10 | 10 | 12 | 10 |
| | | Fluid | 7 | 7 | 8 | 11 | 15 | 20 | 22 | 24 | | | | | | | 22 | 21 | 20 | 14 | | 8 | 7 | 10 | 10 |
| R.B. | † | Serum | 22 | 121 | 64 | 56 | 52 | 150 | 138 | 127 | 118 | | | | | | | | | | | 14 | | | |
| | | Fluid | 9 | 11 | 13 | 18 | 22 | 28 | 39 | 46 | 52 | | | | | | | | | | | 12 | | | |

*Initial dose, 80 gm. (1.5 gm. per kilogram), followed by 40 gm. (0.8 gm. per kilogram) at seven hours
†Initial dose, 40 gm. (0.5 gm. per kilogram), followed by 80 gm. (0.9 gm. per kilogram) at three hours

duction in cerbrospinal fluid pressure occur less than one hour after the urea was started.

The increase in serum urea nitrogen varied from 33 to 257 mg. per cent. There was a distinct lack of correlation between the total quantity or dose per kilogram of urea administered and the initial elevation in serum urea nitrogen. For example, at thirty minutes, the values for J. W. and R. B. are approximately the same despite the fact that the former patient received 2 times the total dose of urea and 3 times as much on the basis of weight.

After the first hour, the fall in serum urea nitrogen was gradual and relatively uniform, but the time required for return to control values varied considerably.

The relationship of serum urea nitrogen to cerebrospinal fluid urea nitrogen in 5 patients is shown in table 3. Cerebrospinal fluid urea concentration shows a gradual increase which approaches the falling concentration in the serum, but the time required for equilibrium is quite variable. In fact, equilibrium was not attained in 2 patients (R. H. and R. B.) during the periods of observation. If this table is compared with the pressure responses, it is evident that there is no uniform correlation between the cerebrospinal fluid pressure and the difference between the serum urea nitrogen and cerebrospinal fluid urea values. Thus, in patient A. A., equilibrium was approached eleven hours after the beginning of the infusion but the cerebrospinal fluid pressure remained normal for several days. In contrast, in patient R. B., the pressure was higher than the control level at a time (three hours) when the serum urea nitrogen was still significantly greater than the cerebrospinal fluid urea.

Table 4 shows the osmolality in serum and cerebrospinal fluid of the same 5 patients in Table 3. Initially, there is a rapid increase in osmolality which parallels the increase in serum urea nitrogen. However, in all except 1 patient (J. W.), the osmolalities of the serum and cerebrospinal fluid reach equilibrium more rapidly than the urea values. Thus, during the first few hours, there is a better correlation between the cerebrospinal fluid pressure and the difference in osmolalities than there is between cerebrospinal fluid pressure and the difference in urea concentrations in serum and cerebrospinal fluid. Nevertheless, neither the

TABLE 4

SERUM AND CEREBROSPINAL FLUID OSMOLALITY

| Patient | Dose of urea | | Control | Time (hours) after beginning of urea infusion | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | ½ | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 7½ | 8 | 9 | 10 | 10½ | 11 | 12 | 13 | 24 | 36 | 48 | 72 | 96 | 120 |
| W.D. | 80 gm. (1.2 gm. per kg.) | Serum | 258 | 340 | 295 | 290 | 290 | 285 | 279 | 276 | 276 | | | | | | | | | | | | | |
| | | Fluid | 261 | 272 | 280 | 290 | 288 | 286 | 290 | 287 | 290 | | | | | | | | | | | | | |
| R.H. | 80 gm. (1.4 gm. per kg.) | Serum | 269 | 309 | 307 | 305 | 309 | 303 | 300 | 299 | | | | | | | | 317 | 313 | | | | | |
| | | Fluid | 281 | 277 | 280 | 289 | 295 | 297 | 296 | 299 | | | | | | | | 315 | 304 | | | | | |
| J.W. | * | Serum | 290 | 329 | 328 | 331 | 326 | 318 | 309 | | 318 | 318 | 320 | 321 | 322 | | 316 | | | | | | | |
| | | Fluid | 293 | 295 | 310 | 318 | 320 | 310 | 312 | | 317 | 312 | 318 | 316 | 318 | | 307 | | | | | | | |
| A.A. | 40 gm. (0.7 gm. per kg.) | Serum | 291 | 312 | 300 | 305 | 300 | 302 | 300 | 297 | | | | | | | 290 | 289 | 286 | 284 | | 283 | 289 | 284 | 286 |
| | | Fluid | 286 | 292 | 290 | 295 | 301 | 303 | 299 | 300 | | | | | | | 297 | 299 | 300 | 294 | | 290 | 292 | 291 | 289 |
| R.B. | † | Serum | 309 | 344 | 312 | 312 | 311 | 334 | 340 | 325 | 321 | | | | | | | | | | | 297 | | | |
| | | Fluid | 298 | 301 | 302 | 313 | 307 | 318 | 320 | 328 | 322 | | | | | | | | | | | 302 | | | |

*Initial dose, 80 gm. (1.5 gm. per kilogram), followed by 40 gm. (0.8 gm. per kilogram) at seven hours
†Initial dose, 40 gm. (0.5 gm. per kilogram), followed by 80 gm. (0.9 gm. per kilogram) at three hours

TABLE 5

SERUM AND CEREBROSPINAL FLUID SODIUM (MILLIEQUIVALENTS PER LITER)

| Patient | Dose of urea | | Time (hours) after beginning of urea infusion | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Control ½ | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 7½ | 8 | 9 | 10 | 10½ | 11 | 12 | 13 | 24 | 36 | 48 | 72 | 96 | 120 |
| W.D. | 80 gm. (1.2 gm. per kg.) | Serum | 143 | 136 | 147 | 149 | 147 | 149 | 145 | 147 | 149 | | | | | | | | | | | | | |
| | | Fluid | 151 | 156 | 156 | 154 | 156 | 162 | 154 | 151 | 154 | | | | | | | | | | | | | |
| R.H. | 80 gm. (1.4 gm. per kg.) | Serum | 139 | 141 | 145 | 141 | 143 | 121 | 147 | 147 | | | | | | | 153 | | 148 | | | | | |
| | | Fluid | 148 | 145 | 145 | 147 | 148 | 151 | 149 | 152 | | | | | | | 151 | | 147 | | | | | |
| J.W. | * | Serum | 142 | 148 | 148 | 142 | 142 | 142 | 142 | | 146 | 142 | 144 | 142 | 142 | 142 | | | | | | | | |
| | | Fluid | 148 | 146 | 148 | 148 | 148 | 148 | 146 | | 148 | 142 | 148 | 145 | 142 | 144 | | | | | | | | |
| A.A. | 40 gm. (0.7 gm. per kg.) | Serum | 160 | 164 | 160 | 159 | 160 | 162 | 160 | | | | | | | 164 | 162 | 158 | 160 | 156 | 150 | 155 | 143 | 145 |
| | | Fluid | 160 | 162 | 162 | 164 | 164 | 164 | 160 | | | | | | | 154 | 154 | 152 | 150 | 150 | 156 | 153 | 152 | 149 |
| R.B. | † | Serum | 143 | 139 | 114 | 147 | 153 | 149 | 149 | 147 | 149 | | | | | | | | | | 137 | | | |
| | | Fluid | 157 | 159 | 159 | 163 | 155 | 165 | 163 | 153 | 153 | | | | | | | | | | 127 | | | |

*Initial dose, 80 gm. (1.5 gm. per kilogram), followed by 40 gm. (0.8 gm. per kilogram) at seven hours
†Initial dose, 40 gm. (0.5 gm. per kilogram), followed by 90 gm. (0.9 gm. per kilogram) at three hours

secondary elevation nor the prolonged reduction of cerebrospinal fluid pressure observed in several patients is adequately explained by these values for osmotic pressure.

Sodium levels were obtained at frequent intervals in blood and cerebrospinal fluid in these same 5 patients (Table 5). Although there are relatively large changes in sodium, particularly in the serum, there is no consistent trend. The 2 grossly abnormal serum sodium determinations in Table 5 undoubtedly represent laboratory errors.

In order to ascertain the laboratory error to be expected in the various chemical determinations, control values were measured in 2 patients. Cerebrospinal fluid and blood were obtained and divided into 5 samples. The urea nitrogen, sodium, and osmolality of each sample were determined and are recorded in Table 6. The urea determinations were quite consistent. The maximal range of error of sodium within any group of 5 samples was 4.1% and osmolalities, 1.7%. Both of these figures are within the range of error expected by the laboratory which performed the determinations.

**Urine determinations.** Urine volume and urea excretion were measured in several patients (Table 7). In all patients, there was a prompt diuresis after administration of urea, which was maximum during the first hour and then rapidly subsided. Of interest is the observation that, despite 40 to 80 gm. of exogenous urea, the twenty-four-hour excretion of urea often did not exceed 30 gm., which is the average normal daily excretion. The patient (E. H.) who received 160 gm. of urea excreted only 55 gm. in twenty-four hours. Since all of the patients were quite ill, this is probably a manifestation of impaired glomerular filtration rate; indeed, 3 patients also had elevated control serum urea nitrogen values. No significant correlation exists between the cerebrospinal fluid pressure response and either the volume of urine or quantity of urea excreted.

**Clinical status of patients.** Table 8 lists the principal diagnoses in the 10 patients. All were semicomatose or comatose except the 2 patients with pseudotumor cerebri. In none of the former group was there a significant change in level of consciousness, as deter-

TABLE 6
CONTROLS

| Patient | Serum Urea | Serum Sodium | Serum Osmolality | Cerebrospinal Fluid Urea | Cerebrospinal Fluid Sodium | Cerebrospinal Fluid Osmolality |
|---|---|---|---|---|---|---|
| 1 | 10 | 147 | 286 | 9 | 145 | 294 |
| 2 | 10 | 150 | 285 | 9 | 139 | 293 |
| 3 | 10 | 148 | 287 | 9 | 139 | 295 |
| 4 | 10 | 150 | 288 | 9 | 145 | 293 |
| 5 | 10 | 150 | 286 | 9 | 145 | 295 |
| *Patient 2* | | | | | | |
| 1 | 12 | 147 | 298 | 10 | 149 | 298 |
| 2 | 12 | 143 | 296 | 10 | 149 | 297 |
| 3 | 12 | 145 | 301 | 10 | 147 | 298 |
| 4 | 12 | 143 | 296 | 10 | 149 | 297 |
| 5 | 12 | 145 | 296 | 10 | 145 | 301 |

mined by response to a painful stimulus, during either the time of maximal reduction of cerebrospinal fluid pressure or the period of secondary rise in pressure. Since none of these patients had marked increased intracranial pressure, it is unlikely that brain edema was the principal cause of their depressed level of consciousness; it is therefore not surprising that urea failed to produce distinct improvement.

## DISCUSSION

Urea produced a prompt and rapid fall in intracranial pressure in each subject. Among the variables which might be expected to influence this response are the dose, concentration, and rate of administration of the solution and the initial cerebrospinal fluid pressure. The concentration and rate of administration in this series were approximately the same in all patients, but the dose ranged between

TABLE 7
URINE VOLUMES AND UREA EXCRETION

| Patient and total urea dose | | Time (hours) 1 | 2 | 3 | 4 | 5 | 6 | 7 | 24 |
|---|---|---|---|---|---|---|---|---|---|
| F.B. 80 gm. | Volume (cc.) | 475* | 725 | 785 | | | 1,285 | | 2,185 |
| | Urea (gm.) | 3.1 | 5.6 | 6.3 | | | 12.3 | | 26.2 |
| G.F. 80 gm. | Volume (cc.) | 450 | 720 | 930 | 1,105 | 1,245 | 1,335 | 1,425 | 2,080 |
| | Urea (gm.) | 4.4 | 8.2 | 11.7 | 14.7 | 17.2 | 19.0 | 20.8 | 35.5 |
| E.K. 40 gm. | Volume (cc.) | | | | | | | | 3,565 |
| | Urea (gm.) | | | | | | | | 30.6 |
| E.H. † | Volume (cc.) | 650 | 1,000 | 1,210 | 1,410 | 1,560 | | 1,805 | 3,995 |
| | Urea (gm.) | 4.0 | 8.0 | 10.9 | 13.8 | 16.2 | | 20.4 | 55.5 |
| B.H. 80 gm. | Volume (cc.) | 445 | 735 | 985 | 1,175 | 1,360 | 1,480 | 1,605 | 2,615 |
| | Urea (gm.) | 2.8 | 4.7 | 6.7 | 8.5 | 10.5 | 11.6 | 12.7 | 19.2 |
| M.D. 80 gm. | Volume (cc.) | | | | | | | 2,300 | |
| | Urea (gm.) | | | | | | | 25.3 | |
| R.H. 80 gm. | Volume (cc.) | | | | | | | 1,300 | |
| | Urea (gm.) | | | | | | | 16.5 | |

*Figures represent total excretion from beginning of urea infusion to time as indicated.
†Patient received 80 gm. of urea initially and an additional 80 gm. between seven and ten hours.

TABLE 8
DIAGNOSIS AND LEVEL OF CONSCIOUSNESS

| *Patient* | *Primary diagnosis* | *Level of consciousness* |
|---|---|---|
| F.B. | Ruptured intracranial aneurysm | Semicomatose |
| G.F. | Head trauma | Semicomatose |
| E.K. | Craniopharyngioma | Comatose |
| E.H. | Metastatic carcinoma, primary unknown | Comatose |
| B.H. | Glioblastoma multiforme | Comatose |
| W.D. | Head trauma | Semicomatose |
| R.H. | Metastatic carcinoma, primary lung | Semicomatose |
| J.W. | Glioblastoma multiforme | Semicomatose |
| A.A. | Pseudotumor cerebri | Alert |
| R.B. | Pseudotumor cerebri | Alert |

0.5 and 1.5 gm. per kilogram. No distinct dose-effect correlation is apparent, but there is the suggestion that reduction in pressure is more pronounced if the initial pressure is elevated.

Other factors which could influence the response to urea are the systemic arterial and venous pressure, the type and extent of central nervous system pathology present, and the patient's general physical condition. Fremont-Smith and Merritt[31] did not find a correlation between arterial and cerebrospinal fluid pressures in a large series of patients; that is, neither the systolic nor diastolic pressure affected the cerebrospinal fluid pressure nor did cerebrospinal fluid pressures up to 800 mm. of water appear to alter arterial pressures. Weed and Hughson[32] found that the cerebrospinal fluid pressure response to hypotonic and hypertonic solutions was relatively independent of venous and arterial tension. However, Luttrell, Finberg, and Drawdy[33] described a marked fall in arterial and venous pressures in cats which received doses of hypertonic urea approximately 5 times the average dose used in the present study. In regard to the patient's brain pathology and general physical status, the numerous variables are difficult to assess. Probably, such considerations as the volume of intracranial space occupied by tumor, the amount of edema present, and the patient's electrolyte status are important, but the influence of these factors on cerebrospinal fluid pressure responses to urea is unknown.

The secondary elevation of cerebrospinal fluid pressure observed in this study does not appear to have been previously described with urea.* Whether this phenomenon is of clinical significance is problematic. In the 3 patients in whom the maximal secondary elevation was 100 mm. of water, it is unlikely that this produced any deleterious effect. However, in a fourth patient, the cerebrospinal fluid pressure was initially 150 mm. and ultimately rose to over 400 mm. of water. Although there was no apparent change in the patient's clinical status, such a marked and relatively rapid increase in intracranial pressure is potentially dangerous. I do not believe that these observations contraindicate the use of this agent but wish to emphasize that urea, as virtually every other compound used for this purpose, will occasionally produce a marked reactive increase in intracranial pressure.

Any hypothesis of the mechanism of action of urea should account for its property of reducing intracranial pressure and also attempt to explain why prolonged reductions and secondary elevations of pressure occur. Im-

*A secondary elevation in cerebrospinal fluid pressure after urea administration has been described recently by Stubbs and Pennybacker (Lancet 1:1094-1097, 1960).

portant factors in such an explanation are the physicochemical properties of the urea molecule, especially its distribution in blood, brain, and cerebrospinal fluid. Urea is a water-soluble molecule which lacks an ionic charge, is not metabolized by the brain, and does not appear to alter brain function, even in large concentrations. Good evidence exists that urea is secreted into the cerebrospinal fluid by the choroid plexus, and, under physiologic conditions, the ratio of the concentration of urea in cerebrospinal fluid to its concentration in blood is about 0.8:1.[34] This is the steady state for urea across the blood–cerebrospinal fluid barrier and presumably is maintained by a balance between the secretion of the choroid plexus and absorption through the arachnoid villi. Whether a similar equilibrium exists between the blood and extracellular space of the brain is unknown. (The term "extracellular space" is used in this discussion with cognizance of the fact that there is controversy about the existence of such a compartment in the brain.)

It has been demonstrated that sodium exchange across the blood-brain and blood–cerebrospinal fluid barriers occurs at the same rate,[35] as is the case for chloride, bromide, iodide, and thiocyanate.[36] However, this is not true of urea. Recently, Schooler, Barlow, and Roth[37] investigated the problem using carbon-14 urea and demonstrated that this penetrates the blood–cerebrospinal fluid barrier more slowly than it crosses the blood-brain barrier. Furthermore, there was marked variation in urea concentration in different areas of the brain. The concentration in cerebral cortex exceeded the blood concentration within six hours, but equilibrium between blood and the cerebral white matter was not established until twelve hours after injection. Since tracer doses of carbon-14 urea were used, the blood urea level was never significantly elevated. Several years previously, Riser, Valdiquie, and Guiraud[38] described qualitatively similar results in dogs using large doses of hypertonic urea (2 to 3 gm. per kilogram). They determined blood, cerebrospinal fluid, brain, and muscle concentrations at frequent time intervals and found a rapid elevation of brain urea concentration, approximating the rate of increase in muscle. Urea equilibrium between blood and brain was established between thirty minutes and one hour, in contrast to the six hours required for the earliest blood-brain equilibrium with carbon-14 urea. They also found that urea entered the cerebrospinal fluid from the blood more slowly but that equilibrium was established within three hours, as opposed to the six hours described by Schooler and associates.[37] In part, the quantitative difference in these results can be attributed to the dose of urea administered or, in addition, possibly to the different methods used for urea assay in the two series.

Riser and associates[38] postulated that the difference in the areas of the 2 surfaces of exchange was primarily responsible for the difference in urea concentrations in brain and cerebrospinal fluid rather than a selective permeability of the blood-brain and blood– cerebrospinal fluid barriers. Thus, the rich capillary network of the brain provides a much larger surface area for diffusion of urea than do the capillaries in contact with the cerebrospinal fluid. Also, it has been demonstrated that, when the urea concentration in the blood is increased, it diffuses across the entire blood–cerebrospinal fluid boundary. Thus, the role of the choroid plexus, so important in maintaining the steady-state of urea under physiologic conditions, must be minimal when a large urea diffusion gradient is established between blood and cerebrospinal fluid.

These observations are important in the interpretation of the present results because they may help explain why neither the urea concentrations nor the osmolalities of blood and cerebrospinal fluid correlate with the cerebrospinal fluid pressure changes except during the period of initial fall in pressure. If there is a gross difference between diffusion rates and ultimate concentrations of urea in brain and cerebrospinal fluid, the values for cerebrospinal fluid do not accurately reflect the difference in osmotic pressure between blood and intracranial space. It is apparent that a change in intracranial pressure may occur from an alteration in the volume of the brain and/or cerebrospinal fluid, but, normally, the volume of brain is 6 to 7 times the volume of cerebrospinal fluid and the capillary-brain surface area is greater than the surface area between blood and cerebrospinal fluid. Consequently, if

the osmotic gradients are not the same across the blood-brain and blood–cerebrospinal fluid barriers, the former should show a closer correlation with changes in intracranial pressure.

However, this hypothesis does not explain the rapid increase in cerebrospinal fluid pressure which occasionally follows the initial pressure reduction (R. B., Fig. 3), nor does it explain the secondary elevation in pressure. Evidence exists that urea is distributed throughout most of the extracellular and intracellular space, and urea has been used to measure total body water.[39,40] Equilibrium between the intracellular and extracellular space is established between forty-five minutes and one hour. This period corresponds well with the time required for maximal reduction of cerebrospinal fluid pressure, so it may be assumed that the pressure continues to fall until equilibrium is established. Urea should then diffuse from the intracellular to the extracellular space to the blood, and the rate of diffusion should be proportional to the rate of excretion of urea from the body. At the same time, water diffuses into the brain, tending to restore cerebrospinal fluid pressure to the initial value. If urea equilibrium is not yet established between blood and cerebrospinal fluid, the osmotic gradient for water will still be from cerebrospinal fluid to blood. However, the cerebrospinal fluid pressure is primarily dependent on the fluid volume of the intracranial-spinal space, which is determined by the net sum of the osmotic gradients for water across the blood-brain and blood–cerebrospinal fluid barriers, if the present explanation is correct.

A third factor to be considered is the brain–cerebrospinal fluid boundary. There is reason to believe that, if a substance exists in greater concentration in the brain, diffusion will occur into the cerebrospinal fluid and vice versa, depending on the size and solubility properties of the molecule.[41] Under the present circumstances, urea might pass from brain to cerebrospinal fluid, tending to counteract the diffusion differences between the blood-brain and blood–cerebrospinal fluid barriers. However, there appears to be no specific information on this point.

If the hypothesis is correct that there is slow diffusion of urea from the cells to the extracellular space to the blood, cerebrospinal fluid pressure should return to the initial level quite slowly, since the osmotic gradient for water (blood to brain) during the recovery phase is quite small compared to the osmotic gradient (brain to blood) induced by the loading dose of urea. In some patients, recovery of cerebrospinal fluid pressure required many hours or even days, whereas in others the rise in pressure was rapid. Therefore, an additional hypothesis is required to explain the rapid recovery and also the secondary elevation of cerebrospinal fluid pressure.

Steffenson[39] noted that the estimation of total body water using urea was higher than that calculated with alcohol and suggested that urea attains a higher concentration in the cell than in the extracellular space. This suggestion receives some support from the work of Ralls,[42] who found that the ratio of red blood cell urea per 100 cc. of water to plasma urea per 100 cc. of water was 1.14. He offers as one explanation for this finding a more rapid elimination of urea from plasma than from cells, but this was discounted by observations that, under conditions which permitted decreases and increases in the urea of different portions of the same blood sample, the distribution remained the same as it was in the freshly drawn blood. The best explanation appeared to be fixation of some urea in the cell either by adsorption or chemical union with a cell solute. If this were to occur in brain cells, for example binding of urea with an intracellular protein, it would still not explain the rapid recovery and secondary increase in cerebrospinal fluid pressure because, once bound, the urea would lose virtually all of its osmotic activity. Furthermore, hypertonic saline and sucrose can also produce a secondary rise in pressure, but, for the most part, both sodium and sucrose remain in the extracellular space.

Another possible effect of urea is alteration of the blood-brain and blood–cerebrospinal fluid barriers produced by large concentrations of the drug. If this happened, a disruption of the steady-state equilibrium of other osmotically active substances might occur. This is suggested by the fact that the osmolalities of blood and cerebrospinal fluid reach equilibrium more rapidly than the urea values (Tables 3 and 4). Alterations in barrier per-

meability could be minimal because a relatively small shift in sodium can produce large changes in osmolality. Davson[34] has calculated that a variation in sodium concentration of 5% would create a difference in osmotic pressure of 274 mm. Hg if the membrane between plasma and cerebrospinal fluid were impermeable to the ion. Since the barriers are semipermeable to sodium, the actual difference would be less than the theoretic maximum but still considerable. The laboratory error in the sodium determinations in the present study is about 4%, indicating that a sodium exchange of osmotic significance could have occurred and not have been detected.

However, proof is required that urea, in the concentrations used in this study, alters the blood-brain or blood–cerebrospinal fluid barriers. A variety of different compounds has been injected into the carotid artery in an attempt to break down the blood-brain barrier but without much success. Bile salts[43,44] and acetylcholine[44] will increase barrier permeability to trypan blue and other vital dyes, but lethal doses are often required. Diodrast[45] also causes increased permeability of cerebral capillaries, which is often associated with a temporary disturbance in brain function. Recently, Fishman[46] studied the effect of several compounds on sodium exchange times between blood and cerebrospinal fluid and found that vasopressin and acetazoleamide were the only substances which produced a significant alteration. Large doses of vasopressin increased the exchange rate suggesting increased permeability of the blood–cerebrospinal fluid barrier, whereas acetazoleamide had an opposite effect. Davson and Luck[35] had previously demonstrated that acetazoleamide inhibits the secretion of sodium by the choroid plexus.

In the patients in the present study, chloride and potassium levels were unchanged after urea administration. This agrees with the results of Murphy and Benson,[47] who found no significant variation in serum and cerebrospinal fluid chloride and potassium during a three-hour period after administration of hypertonic urea to 10 patients without central nervous system pathology. Therefore, it seems unlikely that urea alters barrier permeability, but experimental evidence is required.

An additional factor that may contribute to the rapid rise in cerebrospinal fluid pressure is increased secretion of fluid by the choroid plexus secondary to the reduction in intracranial pressure or to a specific effect of the hypertonic agent on the secreting cells. This could occur independently of the difference in osmolality of blood and cerebrospinal fluid.

The absence of correlation between the reduction in cerebrospinal fluid pressure and either the urine volume or urea excretion is not surprising considering the influence on pressure responses of the multitude of variables already discussed. Javid and Anderson[48] found that the cerebrospinal fluid pressure reduction was more prolonged after bilateral nephrectomy, but this represents an extreme situation in which urea loss from the body is minimal. Wilson and associates[49] studied the cerebrospinal fluid pressure response to equiosmolar solutions of sodium succinate, sodium lactate, and sodium chloride. They had anticipated that effectiveness in lowering pressure would be proportional to the respective renal clearances of salt and water, but, in fact, all 3 solutions produced equal lowering of pressure.

Serious sequelae resulting from hypertonic urea are apparently quite uncommon. A patient in this series had transient hemoglobinuria, which has also been described by Javid.[27] He states that this can be prevented by using 10% invert sugar instead of dextrose or saline in the solution. Wise[50] has described a case of hyperosmolarity and azotemia resulting from prolonged oral administration of 30% urea. Of particular interest are the experiments of Luttrell and associates[33] and Girard,[51] in which hyperosmolarity induced by hypertonic saline or urea produced hemorrhagic encephalopathy. Since the lesions were found in animals sacrificed within four hours after urea administration, it appeared that the damage occurred during the precipitous drop in cerebrospinal fluid pressure. Also, cisternal infusion with saline sufficient to prevent a marked fall in pressure prevented these lesions. The dose of urea used in these experiments was considerably higher than the maximal dose advocated in human beings, but the results do suggest that intracranial hemorrhage is a potential complication of large doses of hypertonic agents.

## SUMMARY AND CONCLUSIONS

1. Hypertonic urea administered intravenously produced a rapid and marked fall in cerebrospinal fluid pressure in all patients.

2. The degree of pressure reduction was proportional to the dose only if the level of the initial pressure was also considered.

3. After the initial reduction in pressure, half the patients showed a secondary elevation above control levels.

4. Correlation was lacking between the time required for recovery of cerebrospinal fluid pressure and the urea concentrations and osmolalities of blood and cerebrospinal fluid. Several hypotheses are considered as a possible explanation for these discrepancies.

5. No untoward reactions from the hypertonic urea occurred except transient hemoglobinuria in one patient.

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# Pupillary abnormalities in myasthenia gravis

## Report of a case

Augusto Gentil Baptista, M.D., and
Haroldo Silva e Souza, M.D.

INVOLVEMENT of the intrinsic musculature of the eyes in myasthenia gravis is extremely unusual. Osserman[1] mentions no pupillary abnormality in his 325 patients but admits that, on rare occasion, the pupillary reflex may be sluggish and show exhaustion on persistent stimulation. When they aver that the iris musculature is entirely spared by myasthenia, so that pupillary reflexes remain unaltered, Guillaumat, Morax, and Offret[2] disagree with Osserman, as well as with Marback,[3] who admits the occurrence of internal ophthalmoplegia in myasthenic patients. Analyzing his 300 cases, Grob[4] points out that pupils were never affected and only rarely was difficulty in accommodation observed. In Walsh's experience,[5] the internal musculature of the eye is not involved in myasthenia gravis, and he quotes a paper by Campbell and Bramwell, published in 1900, while mentioning scattered reports of such involvement in the medical literature. Pupillary changes in this condition are so uncommon that, in a patient with external ophthalmoplegia, they are held as a differential diagnostic point against myasthenia.[1,4]

Because of its rarity, we thought it would be of interest to report on a patient with myasthenia who showed involvement of the pupils by the disease.

### CASE REPORT

A 41-year-old, married, Negro farmer was admitted to the hospital on June 3, 1960, with the chief complaint of drooping of the eyelids and loss of muscle power. Eight months previously, he began to feel a decrease in his laboring capacity, more marked by early evening. Some days later, difficulty in completely opening the eyes was first noticed and was attributed to "heaviness" of the lids; this was accompanied by "seeing double." Muscle weakness progressed steadily. The patient's ability to work decreased gradually, as did his capacity to walk long distances and to climb stairs. The lid-drop became so marked as to obliterate vision, partially on the right and almost completely on the left. Diplopia persisted. Three to four months before admission, the patient became first chairridden and, a few weeks later, bedridden. By this time, he was entirely unable to comb his hair and had to manually move his jaw while chewing. Coughing was "weak," but there was no shortness of breath. Occasionally, there would be "blurring" of vision as well as an eight- to ten-day fecal retention, for which difficulty in strongly contracting abdominal muscles was blamed.

On general physical examination, the patient was a rather tall, well-nourished Negro male with acromegaloid facies, bilateral blepharoptosis, divergent strabismus, and drooping jaw (Fig. 1.). If he was forced to a sitting position, the head would lean forward and the spinal column would describe a well-marked curve of posterior convexity. Pulse was 80 and regular, respiration, 21; blood pressure, 150/90; and temperature, 96.8° F. Lungs were clear. Heart sounds and abdomen were normal.

Neurologic examination showed an alert man with normal mentational processes. Speech was slightly slurred, probably due to difficulty in moving the jaw. If helped to a standing position, the patient could barely

From the Department of Internal Medicine, Hospital das Clínicas, Universidade da Bahia, Salvador, Brazil.

balance himself with his feet wide apart and could walk very slowly without lifting them from the ground. While sitting, he was entirely unable to lift the feet to knee level or to clear one thigh at a time from the chair surface. Smell, vision, and hearing were intact, except that he had learned to mentally suppress one image, seeing through the right eye only and thus avoiding diplopia.

On ophthalmoscopic examination, fundi and media were normal. Severe external and internal ophthalmoplegia was noted, more marked on the left (Figs. 1 and 2A). The right eye could move 15° upward and 25° downward; the left eye would barely make 10° of total motion in the up-down direction. In the horizontal plane, each eye could move 15°, equally divided between adduction and abduction. Pupils were dilated and unequal. In semiobscurity, the right pupil measured 6.5 mm. and the left, 9 mm. A 60-watt bulb at a distance of 30 cm. made the right pupil contract to 5 mm. and the left to 7 mm.; response was somewhat sluggish. After three minutes of stimulation, both pupils had dilated back, the right to 6 mm. and the left to 9 mm. (A normal control's pupils were, in semiobscurity, 3.5 mm. in diameter; on identical light stimulation, they came down to 2 mm. and so remained). Accommodation to near vision would produce slight convergence, difficult to elicit due to monocular vision, and minimal, practically immeasurable contraction of the pupils.

The jaw was held partially open due to weakness of masseters and temporals; strength of pterygoids was only slightly decreased. Chewing was difficult. Facial muscles were very weak, giving to the face the known mask-like appearance. Swallowing and palatal motility were unimpaired. The patient could count continuously to over 100 without getting tired. All other muscle groups had their strength diminished to variable degrees: moderate in the forearm muscles, biceps, and extensors of head and severe in triceps, flexors of the head, shoulder-girdle, and lower-limb muscles. He was unable to abduct his arms more than 50° from the lateral thoracic walls. Accentuation of muscle weakness could be easily seen on repeated contractions. Muscle tonus was decreased all over, but there was

Fig. 1. Photograph of patient

no atrophy. Coordination was impaired to an extent compatible with weakness. Tendon reflexes were normal; the knee jerks had a pendular quality. Plantars were flexor. Superficial and deep sensation was unimpaired.

No enlargement of thymus or sella was seen on roentgenograms, but there was widening of the aortic shadow and enlargement of the left ventricle. An electrocardiogram showed an intraparietal block in this ventricle. Pulmonary and pituitary function studies were not carried out. Other laboratory tests were unrevealing.

After intramuscular injection of 1.5 mg. of neostigmine, the patient became able to walk

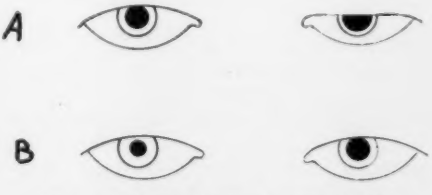


Fig. 2. Diagram of patient's eyes. [A] Before medication. [B] After 1.5 mg. of neostigmine intramuscularly

fairly well. Jaw-drop disappeared, and the arms could be hyperabducted so that the hands could be joined above the head. Power became practically normal in all moderately involved muscles, although there still was residual weakness in all those severely involved. Ptosis disappeared on the right and improved on the left (Fig. 2B). Abduction became normal in both eyes, as did downward movement of the right eye. This eye could move 15° inward and 25° upward. The left eye moved 10° inward, 10° upward, and 25° downward. Pupils decreased in size, the right to 4 mm. and the left to 6 mm. On light stimulation, carried out as before, they contracted to 2 and 2.5 mm., respectively, without redilation on prolonged stimulation. Accommodation also improved, response in each pupil representing a decrease of about 1.5 mm. in its diameter. Once contracted to near vision, they could be further contracted by light.

Pyridostigmin bromide, 3 tablets of 60 mg. each every four hours and then every three hours, induced partial control of symptoms. The effect of the drug was much more prolonged on the pupils than on skeletal muscles. Its action on the latter had already disappeared after the four-hour interval, whereas, even when the patient skipped a dose, going for eight hours without medication, the effect on the pupils was still noticeable.

COMMENT

Tongue and pharyngeal muscles were apparently spared in this fairly severe case of generalized myasthenia gravis, in which even the iris and, possibly, the respiratory muscles were involved. Cardiac findings could be attributed to hypertension, but myasthenia cannot be entirely ignored as the cause since it is known to occur. Several facts point to this disease itself as responsible for the pupillary changes in our patient: [1] absence of any other finding which could explain them; [2] greater mydriasis on the side of the more severe external ophthalmoplegia; [3] fair immediate response to light, with redilation on prolonged stimulation, a phenomenon which parallels the usual normality of tendon reflexes as opposed to the exhaustion of skeletal muscles on repeated or sustained contraction; [4] associated severe impairment of pupillary response on accommodation to near vision; and [5] marked pupillary muscle improvement induced by neostigmine, paralleling that seen in the other involved muscles. Furthermore, mydriasis is what one would expect with involvement of the eye musculature of a diffuse character, such as would result from myasthenia, since the constrictor element is by far the most important in determining pupillary size. The improvement seen after neostigmine cannot be ascribed to the known myotic action of the drug on local application to the eye, since it has no such effect in systemic use[6] at nontoxic doses.

Most authors agree that smooth muscles are spared by myasthenia gravis. Since the iris muscles are smooth, the pupillary abnormalities occasionally observed suggest the possibility of involvement of other smooth muscles, at least in the more severely diseased patients, and make it desirable to carefully study them in this regard. Anatomic alterations in the intramuscular nerve endings have recently been described in myasthenia,[7,8] pointing to these endings as the probable seat of derangement in the condition. The structural differences between the end-plates in striated and smooth muscle would, then, account for the latter being usually untouched. However, since abnormalities in nerve endings occur even in skeletal muscles not clinically weak,[8] one wonders what the search for alterations of a similar nature in smooth muscle will reveal.

The present case offers a possible explanation for the phenomenon observed by Rakonitz[9] in myasthenia, consisting of the pupils being further contracted by light when already contracted on accommodation while the reverse—further contraction on accommodation of pupils already contracted by light—is not observed.[1] Although pupillary response was, in our patient, decreased to both light and accommodation, it was more so to the latter. We would say that Rakonitz saw pupils in the initial stage of involvement, the light reflex still preserved but the accommodation response already impaired. What this means in terms of the physiology of intrinsic eye motility and of the mechanism of myasthenic extension into the iris muscles remains to be determined.

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# Autonomic representation in the human orbitotemporal cortex

J. M. Van Buren, M.D., C. A. Bucknam, M.D.,
and W. L. Pritchard, M.D.

THE AUTONOMIC REPRESENTATION of the orbitotemporal cortex has received intermittent scrutiny since the initial pioneer work of Spencer.[1] More recently, clinical indications including epilepsy and the treatment of pain and psychotic states have permitted an extension of these observations to include man.

In the present study, it has been possible to observe the autonomic responses to orbitotemporal stimulation in a number of patients in whom the mental status was within normal limits and in whom the neurologic and, in some, the subsequent pathologic examination of the brain was normal. This appeared to free us of the problems of epileptic facilitation and the uncertainty of whether the autonomic responses of psychotic individuals are identical with those of normal persons. In addition to observing the effect of stimulation upon several simultaneously recorded autonomic functions, it was possible by this method to examine the functional interrelationships of the responses.

## METHODS

The present material consisted of 11 individuals undergoing either hypophysectomy or hypophyseal stalk section for palliation of metastatic breast carcinoma. Before operation, all patients had a normal neurologic examination, and the electroencephalogram was normal in all but 2. N.B. showed a moderate diffuse dysrhythmia, and A.M. had evidence of a questionable right occipital and left temporal lesion. Premedication consisted of 25 mg. of Phenergan (promethazine), 50 mg. of Demerol (meperidine), and 0.4 mg. of scopolamine. Phenergan was omitted in E.C. and W.E. The anesthetic agents used are indicated in Table 1. The anesthesia was allowed to lighten before the recording period to the point where spontanous movements appeared and then was increased only enough to abolish these movements. In nearly all cases, the operative field was blocked by subcutaneous injection of Nupercaine solution (1:4,000) to assist in maintaining the lightest possible anesthesia consistent with the maintenance of an endotracheal tube. The patients were postured supine with the head slightly extended, and the right orbital surface was exposed by a low frontal craniotomy. The exposure was assisted by withdrawal of spinal fluid. No cortical lesions were seen in any of the exposures.

Stimulation was carried out with a constant current stimulator designed by Mr. George Durek. This provided square wave pulses of 2.5 msec. duration at a frequency of 60 per second. Although stimulation was carried out with a unipolar hand-held electrode, the placing of 500,000 ohms resistance in series with the patient served to reduce the current variations under operating conditions to ±5%. A setting of 0.2 mA could be felt as a very faint tingling sensation and sour taste on the observer's tongue, while currents above 0.5 mA bordered upon a painful sensation on the tongue. Since we were mapping for maximal response, currents between 2 and 4 mA were used. At 4 mA, close observation of the contact of the electrode with the pial surface showed quite obvious gas formation. The use of relatively high current values was induced by our generally negative findings on the pos-

From the Branch of Surgical Neurology, National Institute of Neurological Diseases and Blindness, Bethesda, Md.

TABLE 1
SUMMARY OF CONDITIONS, TYPES OF OBSERVATION, AND AVAILABLE POSTMORTEM FINDINGS

| Name<br>Operation date<br>Number | Agents before recording* | Agents during recording | Recordings taken: Blood pressure | Respiration | Upper Esophagus | Lower Esophagus | Gastric | Plethysmogram | Date of autopsy | Postmortem findings: Central nervous system findings |
|---|---|---|---|---|---|---|---|---|---|---|
| L.B.<br>6/18/59<br>02-38-94 | Fluothane†<br>$N_2O$‡<br>Thiopental | Thiopental | X | X | X | X | | | | |
| N.B.<br>4/22/59<br>02-17-63 | Fluothane<br>$N_2O$<br>Thiopental induction<br>300 mg. | Fluothane<br>$N_2O$ | X | X | X | | X | X | 2/26/60 | Negative |
| E.C.<br>1/29/59<br>02-28-12 | Fluothane<br>$N_2O$<br>Thiopental induction<br>100 mg. | $N_2O$ | X | X | | | | X | 4/7/59 | Negative |
| W.E.<br>3/12/59<br>02-11-67 | $N_2O$<br>Anectine<br>Thiopental | $N_2O$<br>50 mg.<br>Thiopental | | X | | | X | | | Carcinoma in right temporal dura and several small cerebral deposits |
| A.H.<br>1/8/59<br>02-18-75 | $N_2O$<br>Fluothane | $N_2O$<br>Fluothane | X | X | | | X | | 4/17/59 | |
| E.K.<br>6/24/59<br>02-43-89 | Fluothane<br>$N_2O$ | $N_2O$<br>Thiopental<br>50 mg. | X | X | X | | (Cardia)<br>X | | 1/7/60 | Negative |
| C.M.<br>8/27/59<br>00-90-42 | Fluothane<br>$N_2O$ | $N_2O$<br>Thiopental<br>150 mg. | X | X | X | | X | | | |
| A.M.<br>10/13/59<br>02-62-29 | $N_2O$<br>Anectine | $N_2O$<br>Thiopental<br>100 mg. | X | X | X | | X | | 1/19/60 | Negative |
| E.N.<br>3/25/59<br>02-31-05 | Fluothane<br>$N_2O$ | Fluothane<br>$N_2O$ | X | X | X | | | X | 3/7/60 | Negative |
| S.P.<br>3/19/59<br>00-99-79 | $N_2O$<br>Anectine | $N_2O$<br>Demerol | X | X | X | | | X | 6/1/60 | Negative |
| V.V.<br>11/10/59<br>02-12-51 | $N_2O$-Anectine<br>Thiopental<br>Demerol | $N_2O$<br>Thiopental<br>200 mg. | X | X | X | | | | | |

*See text for premedication.
†2-bromo-2-chloro-1:1:1-trifluoro-ethane
‡50 to 70% nitrous oxide and oxygen

terior orbital surface and in an attempt to be certain that the absence of response was not due simply to an inadequate stimulus.

Table 1 indicates the autonomic functions which were well observed in each patient and upon which the present report is based. Blood pressure was recorded from a 16-gauge polyvinyl femoral arterial catheter connected to a Statham P-23AA, P-23BB, or P-23Dc transducer, which was connected to a Sanborn Model 150 amplifier-recorder system. Respiration was recorded from an ordinary accordion-type pneumograph, which was placed over the patient's epigastrium. In this position, the pneumograph was able to monitor movement of the abdominal wall musculature which might have provided confusing artifacts in the intragastric pressure recordings. Esophageal and gastric pressure records were obtained from condom balloons 4 to 6 cm. in length on 16-gauge polyvinyl catheters, which were tied together at convenient intervals. These were passed through the nose and swallowed. The final position of the balloon was determined both by the distance of tubing swallowed and by the characteristic change in the direction of fluctuation of the respiratory artifact as the balloon passed from the thoracic to the abdominal cavities. The exact position of the lower balloon in the stomach was uncertain. In some cases, recordings were made from the upper and lower portions of the esophagus and the gastric recording was omitted. The pneumoplethysmogram was recorded from a finger which was thrust into a glass capsule. The interval between the finger and capsule was oc-

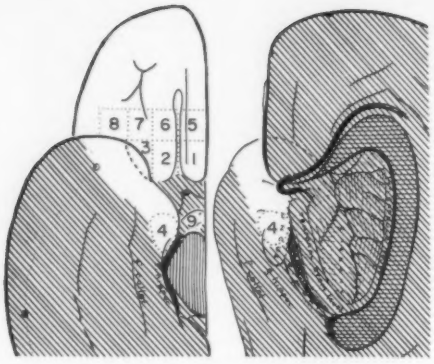


Fig. 1. Areas regularly stimulated in all cases are numbered. Hatching indicates areas not available for stimulation. Unhatched cortex outside numbered areas was stimulated to some degree in each case but not in a systematic fashion. No positive responses were obtained here.

cluded either by plasticine or by a rubber sleeve fitting closely around both the capsule and the finger. No complications resulted from the recording procedures.

RESULTS

The right subfrontal exposure for hypophysectomy or section of the hypophyseal stalk provides easy access to the entire orbital surface on the right side and the gyrus rectus on the left. The region of the area perforata is protected by a fold of the posterior portion of the orbital surface and a bridging arachnoid membrane, so that exploration on the orbital surface posterior to the anterior portion of the olfactory trigone was not considered desirable. By careful retraction, the mesial aspect of the temporal lobe may be visualized as far posteriorly as the uncus.

The mesial temporal region contains an area from which distinct autonomic responses were obtained on stimulation in all but one patient (W.E.). This region lies immediately lateral to the posterior extremity of the anterior clinoid process and consists in the anterior portion of the uncus and its junction with the hippocampal gyrus (Fig. 1, area 4). Since the posterior portion of the uncus was not visualized, the posterior extension of this responsive area was uncertain, but movement of the stimulating electrode further forward on the confluence of the hippocampal gyrus with the temporal tip, or inferolaterally, on to the hippocampal gyrus itself resulted in negative responses.*

Little of the external surface of the hypothalamus presented for stimulation, but, during exposure of the hypophyseal stalk, the right side of the infundibulum could be stimulated by curving the electrode tip and passing it under the chiasm. The optic nerves and chiasm itself were not stimulated.

Figure 1 illustrates the region on the right side which was available for stimulation, and the areas indicated by numbers were stimulated at least twice in all patients (area 4 in S.P. was omitted due to difficulty in exposure). The areas not included in the boxes were irregularly stimulated, and, since negative responses were the rule, they were not systematically pursued. Particular interest, however, centered upon the environs of area 4 (Fig. 1) on the mesial temporal lobe, and adjacent areas of the inferior temporal tip were stimulated in nearly all patients without evident autonomic responses.

**Orbital surface responses.** Under the present conditions of observation, autonomic responses to stimulation of the available orbital surface were few in number and slight in degree. The positive responses are summarized in Table 2. Slight bradycardia was observed in 2 patients, inhibition and augmentation of respiration in 2 patients, respectively (Fig. 2), and esophageal contractions in 1 patient.

**Hypothalamic responses.** Despite the fact that stimulation was carried well up the hypophyseal stalk to the inferolateral aspect of the infundibulum and the hypothalamic surface overlying the tuberal nuclei, there was only 1 instance when a positive response appeared (A.H.: decrease of inspiratory amplitude and slight fall of baseline of gastric recording). However, the mechanical stimulation coincident with the exposure coagulation and sectioning of the hypophyseal stalk induced a variety of changes in 1 instance (Fig. 3), although this observation was unique in the present series.

*Wall and Davis[2] report that in lower primates autonomic responses were absent on stimulation of the hippocampus, although some appeared from the anterior hippocampal gyrus.

TABLE 2
POSITIVE RESPONSES FROM ORBITAL SURFACE STIMULATION

| *Name* | *Area** | *Current (mA)* | *Duration (seconds)* | *Blood pressure* | *Pulse* | *Respiration* | *Upper esophagus* | *Lower esophagus* | *Stomach* | *Plethysmogram* |
|---|---|---|---|---|---|---|---|---|---|---|
| W.E. | 1 | 2 | 10 | — | — | Apnea for 1 respiration | — | — | Nil | — |
| | 1 | 2 | 10 | — | — | Apnea for 1 respiration | — | — | Nil | — |
| L.B. | 3 | 4 | 10 | Slight rise | Nil | Nil | Nil | Contraction | — | — |
| | 3 | 4 | 11 | Slight rise | Nil | Nil | Contraction | Contraction | — | — |
| E.K. | 5 | 4 | 17 | Nil | 5 second fall during stimulus | Nil | Nil | — | Nil | — |
| | 8 | 4 | 10 | Nil | Slight fall during stimulus | Nil | Nil | Nil | Nil | — |
| S.P. | 5 | 2 | 7 | Nil | Nil | Increased amplitude | Nil | — | — | Nil |
| | 5 | 2 | 10 | Nil | Nil | Increased amplitude | Nil | — | — | Nil |

*Area numbers are diagrammed in Figure 1.

**Mesial temporal responses.** The effects of stimulation in the vicinity of the anterior portion of the uncus and the immediately adjacent transitional temporal cortex were well marked and peculiarly constant (Table 3).

The most prominent response was inhibition of respiration. Stimuli of liminal intensity resulted in a decrease in amplitude of inspiration with or without a diminution in frequency (Fig. 4). With an increase in the intensity of stimulation the inhibitory effect became progressively more marked until apnea supervened. Apnea might occur in any phase of respiration, that is, inspiration, expiration, or at a point part way in the cycle. In a given individual, the phase of respiratory arrest tended to be reproduced on successive stimuli, but well defined exceptions occurred. In most cases, there was a definite latency of the response, which might amount to five seconds or more, and the apnea in many cases would outlast the interval of stimulation by prolonged periods (that is, one minute). The response to stimulation was not constant and would show progressive lessening of the duration and intensity of the response on repeated stimulation. However, the original character of the response could possibly be restored by increas-

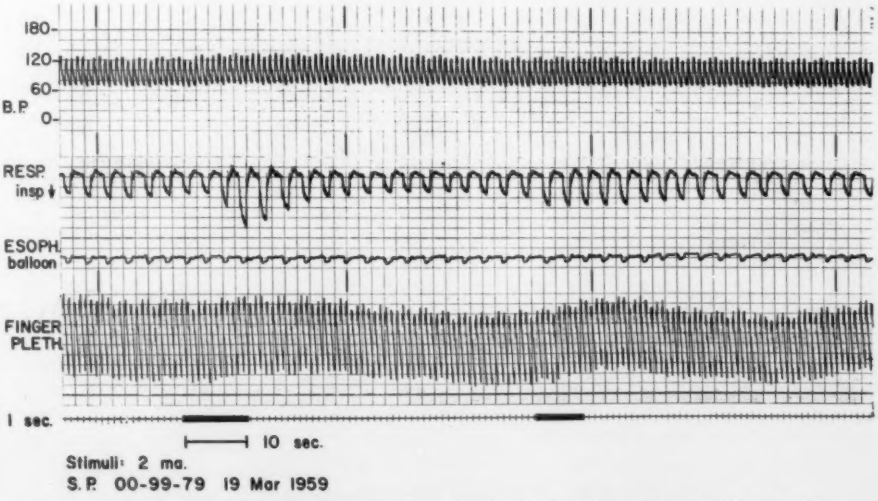


Fig. 2. Increase in amplitude of inspiration associated with stimulation of area 5 (see Fig. 1)

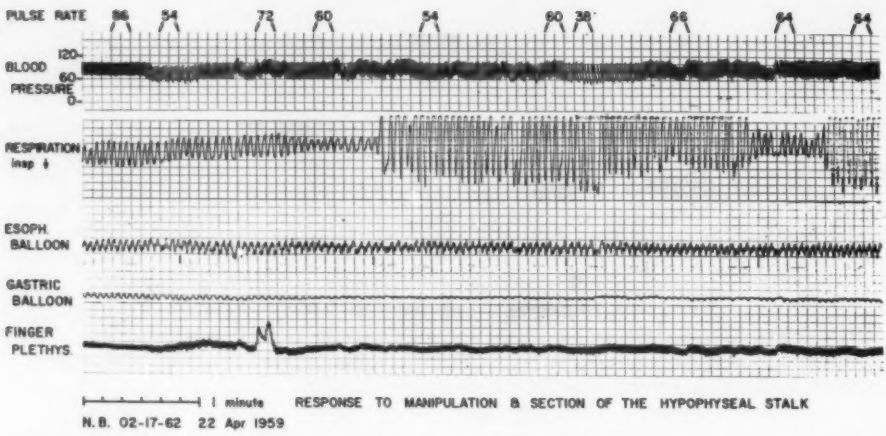


Fig. 3. Changes in blood pressure, pulse rate, and respiration from mechanical manipulation of hypophyseal stalk. In most cases, such changes were slight or absent.

TABLE 3

POSITIVE RESPONSES FROM AREA 4 IN MESIAL TEMPORAL REGION

| *Name* | *Current (mA)* | *Duration (seconds)* | *Blood pressure* | *Pulse* | *Respiration* | *Upper esophagus* | *Lower esophagus* | *Stomach* | *Plethysmogram* |
|---|---|---|---|---|---|---|---|---|---|
| L.B. | 4 | 11 | Nil | Nil | Mid-inspiration apnea | Contraction | Contraction | — | — |
| | 4 | 12 | Nil | Nil | Inspiration apnea | Contraction | 5 contractions | — | — |
| | 4 | 11 | Nil | Nil | Fall in amplitude | Contraction | Nil | — | — |
| N.B. | 2 | 9 | Nil | Slight fall | Inspiration apnea | Nil | — | Nil | Nil |
| | 2 | 34 | Nil | Slight fall | Inspiration apnea | Nil | — | Nil | Nil |
| | 2 | 14 | Nil | Slight fall | Inspiration apnea | Nil | — | Nil | Nil |
| | 2 | 12 | Nil | Slight fall | Inspiration apnea | Nil | — | Nil | Nil |
| E.C. | 2 | 20 | Slight fall | Fall | Mid-expiration apnea | — | — | — | Nil |
| | 2 | 17 | Slight fall | Fall | Mid-expiration apnea | — | — | — | Nil |
| | 1 | 13 | Nil | Nil | Decrease amplitude | — | — | — | Nil |
| | 1 | 18 | Nil | Nil | Decrease amplitude | — | — | — | Nil |
| A.H. | 2 | 15 | Slight rise | Slight rise | 85 second inspiration apnea | — | — | Started contractions | — |
| | 2 | 12 | Nil | Nil | Decrease amplitude | — | — | Fall baseline | — |
| | 2 | 7 | Slight rise | Slight rise | 50 second inspiration apnea | — | — | Started contractions | — |
| E.K. | 4 | 10 | Slight fall | Fall | 89 second mid-inspiration apnea | Contraction | Fall baseline† | — | — |
| | 2 | 10 | Nil | Nil | Expiration apnea | Nil | Nil | — | — |
| | 4 | 10 | Slight fall | Fall | 85 second expiration apnea | Contraction* | Fall baseline | — | — |
| | 4 | 10 | Fall | Fall | 60 second mid-expiration apnea | Contraction* | Fall baseline | — | — |

TABLE 3—(continued)
POSITIVE RESPONSES FROM AREA 4 IN MESIAL TEMPORAL REGION

| Name | Current (mA) | Duration (seconds) | Blood pressure | Pulse | Respiration | Upper esophagus | Lower esophagus | Stomach | Plethysmogram |
|---|---|---|---|---|---|---|---|---|---|
| C.M. | 2 | 16 | Nil | Nil | 95 second mid-expiration apnea | Nil | — | Contractions during apnea | — |
| | 2 | 14 | Slight fall late | Slight fall late | 15 second mid-inspiration apnea | Nil | — | Contractions | — |
| | 3 | 14 | Fall | Fall | 90 second inspiration apnea | Nil | — | Considerable contractions | — |
| A.M. | 4 | 11 | Fall | Fall | 50 second mid-inspiration apnea | Contraction | — | Nil | — |
| | 4 | 8 | 15 second fall | 15 second fall | 7 second inspiration apnea | ?Contraction | — | Nil | — |
| | 4 | 5 | Fall | Fall, decrease amplitude | 13 second mid-inspiration apnea | Nil | — | Nil | — |
| | 4 | 20 | Fall at start and end of stimulus | Fall at start and end of stimulus | 24 second mid-inspiration apnea | Late contraction | — | — | — |
| | 4 | 7 | Nil | Very slight fall | 4 second expiration apnea | Late contraction | — | — | — |
| | 4 | 8 | Fall | Fall | Nil | Late contraction | — | — | — |
| | 4 | 6 | Fall | Fall | Nil | Late contraction | — | — | — |
| | 4 | 11 | Slight fall | Fall | 12 second mid-expiration apnea | Nil | — | — | — |
| E.N. | 2 | 10 | Nil | Nil | Mid-expiration apnea | Nil | — | — | — |
| | 2 | 14 | Nil | Late fall | Expiration apnea | Late contraction | — | — | — |
| | 2 | 14 | Nil | Nil | Decrease amplitude | Late contraction | — | — | — |
| | 2 | 10 | Nil | Late slight fall | Expiration apnea | Nil | — | — | — |
| | 2 | 11 | Nil | Fall | Nil | — | — | — | — |
| | 2 | 8 | Nil | Fall | Arrest for 1 respiration | Nil | — | — | — |
| V.V. | 4 | 15 | Fall | Fall | 63 second late mid-expiration apnea | Contractions | — | — | — |
| | 4 | 16 | Fall | Fall | 14 second mid-expiration apnea | Late contraction | — | — | — |
| | 4 | 10 | ? Nil | ? Nil | Expiration apnea during stimulation | Nil | — | — | — |
| | 4 | 12 | Nil | Nil | Decrease amplitude and frequency | Nil | — | — | — |
| | 4 | 15 | Nil | Nil | Decrease amplitude and frequency | Nil | — | — | — |

*Cardia recorded
‡No laryngeal movement observed

ing the intensity of the stimulating current.

Changes in pulse rate not infrequently accompanied the alterations in respiration and usually consisted of bradycardia (Fig. 4). The time of onset of bradycardia usually coincided with that of respiratory inhibition, although the effect was never as prolonged. In 2 patients (E.N. and N.B.), short bouts of bradycardia occurred in the minute following stimulation. Since similar episodes had not been noted in the earlier record, they appeared related to the stimulation. In 1 patient (A.H.), a mild tachycardia (rise from 76 to 88 per minute) appeared during prolonged bouts of apnea. The tachycardia, with a mild rise in blood pressure, appeared fifteen to thirty seconds after onset of apnea.

Changes in blood pressure were not of

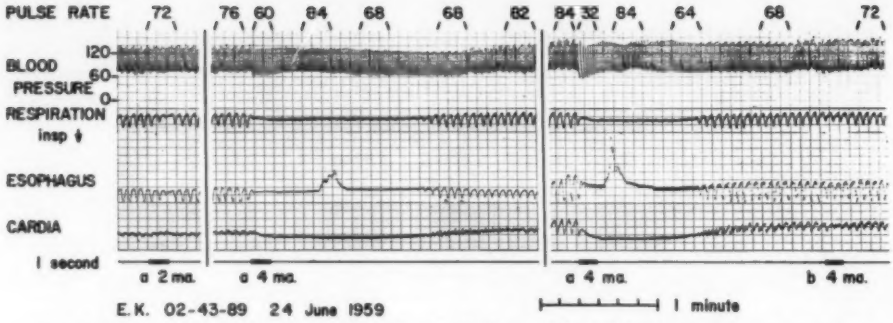


Fig. 4. Effects of liminal and supraliminal stimuli of area 4 (a). Stimulation 5 mm. anterior on temporal lobe (b) gave only doubtful response. Note how long apnea outlasts stimulation period (see Fig. 1).

striking degree and usually consisted of a fall which appeared secondary to alterations in pulse rate. The lack of alteration in the finger plethysmogram under the present conditions suggested that no striking changes in the peripheral somatic vascular system resulted from stimulation.

Esophageal contractions were frequent during or after inhibition of respiration. Careful observation of the throat for the laryngeal movements of swallowing was not carried out in all cases, but, in a number of instances, the esophageal contractions occurred without the preceding characteristic laryngeal movements. This was not unexpected, since the independence of the laryngeal and esophageal components of deglutition may be demonstrated in the conscious subject (Fig. 5). Esophageal contractions appearing a considerable time after stimulation (one to three minutes) were not infrequently observed, and their relationship to stimulation was difficult to determine. The light anesthesia and the presence of both an endotracheal tube and a bolus in the esophagus might well cause sufficient oropharyngeal stimulation to require very little additional central excitation to set off the esophageal contractions. In an instance with both recording balloons in the esophagus, a difference in amplitude of the contractions was evident (Fig. 6). Recording at the level of the cardia (Fig. 4) showed only relaxation of this area after contraction in the esophagus above. Contraction of the stomach followed stimulation in 2 cases and persisted for a period of several minutes thereafter as two- to three-per-minute peristaltic contractions. These contractions were irregular in A.H. and rhythmic in C.M. (Fig. 7). In C.M., the increased gastric contractions were not preceded by evidence of esophageal peristalsis.

## DISCUSSION

In the present observations, general anesthesia was indicated by the clinical circumstances. Although this certainly introduces a profound modification in the degree, at least, of the autonomic responses to stimulation, disadvantages also appear with the use of a heavily sedated patient under local anesthesia or an unsedated patient under local anesthesia who is required to bear the emotional stress of an intracranial procedure under these conditions.

Experience with conscious subjects[3–5] has indicated that the finger plethysmogram reacts to minor stress and a variety of other conditions nearly as readily as changes appear in skin resistance. Under anesthesia, the finger pulsations were of small amplitude (which apparently was the cause of our failure to obtain adequate recordings in a number of cases) and, when adequately recorded, proved unresponsive to stimulation including painful stimuli (stimulation of falx and large veins). Pool[6] briefly mentions the recording of the pneumoplethysmogram during orbitotemporal stimulations in patients with Pentothal, nitrous oxide, and oxygen anesthesia but does not report upon these observations in detail apart

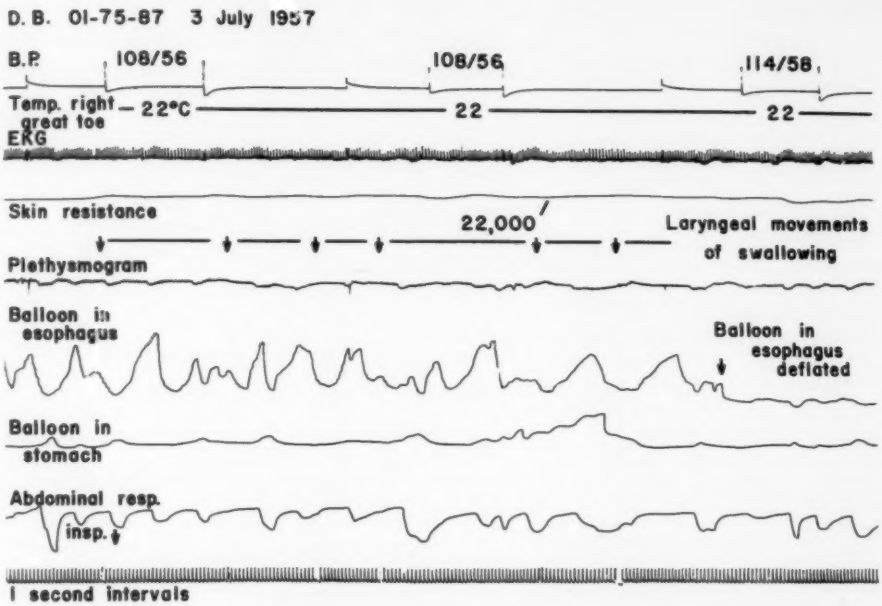


Fig. 5. Esophageal response to mild distention of esophagus in unanesthetized normal subject. Note independence of laryngeal movements of swallowing and esophageal peristalsis. Mild increase in gastric contractions appeared late in series of esophageal contractions. Both gastric and esophageal contractions subsided after majority of pressure in esophageal balloon was released.

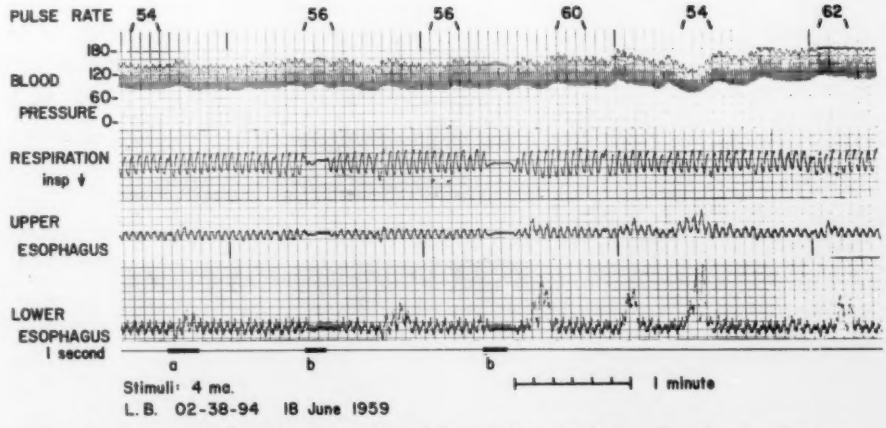


Fig. 6. Contrasting effect of area 3 (a) and area 4 (b) stimulation. Stimulus duration is indicated on signal line (see Fig. 1).

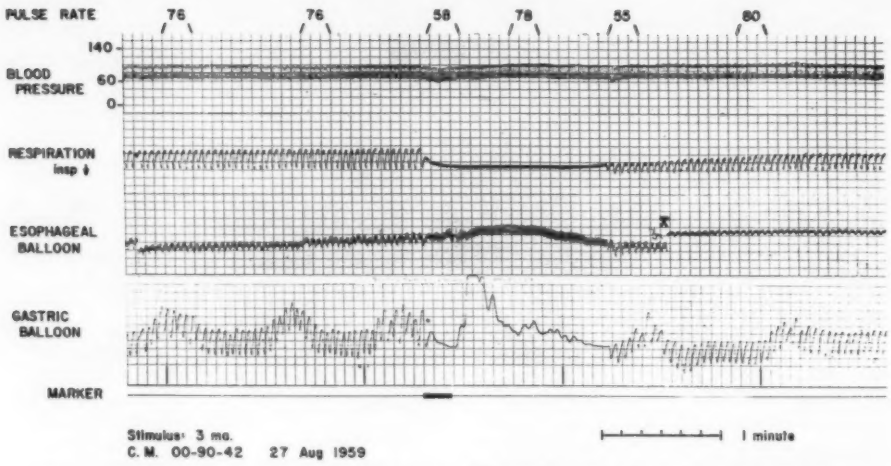


Fig. 7. Stimulation of area 4 (see Fig. 1). Note that gastric peristalsis may increase without preceding esophageal contractions. Fatigue of region was apparent on a repeated stimulation. Intensity of original response was later regained by increasing stimulating current (gain on esophageal balloon reduced at X).

from mentioning that a decrease might occur.

Interpretation of the effects of cortical stimulation upon the esophagus and stomach is beset with numerous difficulties due to the considerable autonomy of these structures. Reversal of the motor effect of vagal and splanchnic stimulation upon the stomach may occur simply on the basis of the preexisting functional state of the viscus.[7-9] Anesthetics profoundly influence the reactivity, and barbiturates in particular have been found to suppress gastric responses to cortical stimulation in animal experiments.[10-14] It is perhaps significant in this connection that barbiturates may possess a relatively selective ability to depress the hypothalamus.[15,16]

Despite our own difficulty in eliciting definite autonomic responses from the posterior orbital cortex,[17, 18] changes in respiratory activity from stimulation of this area in monkey and man have been reported by several authors. The prominent respiratory response has been inhibition. Chapman and associates[19, 20] report predominantly expiratory apnea in man, while Delgado and Livingston[21] found in monkeys that arrest might occur at any stage in the cycle. The response of the blood pressure varied, and both pressor and depressor responses have been reported.[19-22] Bradycardia was not reported to be a part of the depressor response by these authors and, from the published records, apparently was not an obvious component. However, bradycardia was reported in man by Henry, Scoville, and Dunsmore[23] and Pool.[6] Sachs, Brendler, and Fulton[24] found that the respiratory and vasomotor effects were independent manifestations in monkeys and were unaffected by bilaterial vagotomy, splanchnicectomy, adrenalectomy, or destruction of nucleus paraventricularis hypothalami. Pool[6] also found changes in respiration and blood pressure to be independent in man, which is in agreement with our findings. Wall and Davis[2] suggest that the respiratory and blood pressure responses elicited from the orbital surface follow different descending pathways.

Autonomic effects have been more readily obtained from stimulation of the anterior medial temporal lobe. The region about the uncus has the lowest threshold, which approaches the threshold of the premotor cortex.[2, 6, 9, 25, 26] Kaada[9] indicates that, in patients with local anesthesia, the area from which respiratory inhibition may be obtained extends over a considerably wider area than was apparent in the present study. The characteris-

tics of the respiratory and blood pressure responses to stimulation are similar to those from the orbital cortex. Kaada[9] adds the interesting observation that expiratory apnea induced by stimulation here could be voluntarily overcome by the patient. This observation has been recently confirmed both during induced temporal lobe seizures and stimulation in the vicinity of the amygdaloid nucleus in man.[3-5] Drowsiness or impairment of consciousness is reported the inhibitory effect of posterior area.[17, 27] Hoffman and Rasmussen[28] report that stimulation of the temporal pole and posterior orbital region in monkeys inhibits gastric peristalsis and induces a fall in gastric tonus which may accompany hypotension and respiratory inhibition. Bailey and Sweet[22] also reported the inhibitory effect of posterior orbital stimulation on the stomach in the monkey. Further evidence of a predominantly inhibitory action on the stomach of stimulation of the homologue of the primate orbital region in carnivores was supplied by Babkin and associates.[10, 29] In view of this background, the well-defined increase in gastric motor activity obtained in 2 patients in the present series was surprising. In both, there was background gastric peristaltic activity. No responses were seen in patients without preexisting peristaltic activity.

The similarity of the responses elicited in the present material to those produced by afferent stimulation of peripheral nerves in carnivores may be pointed out. Afferent stimulation of the superior laryngeal nerve in dogs has long been known to initiate deglutition.[30] More recently, however, it has been demonstrated[29] that afferent stimulation of both the superior laryngeal nerve and vagosympathetic trunk in the dog initiated a response which in its entirety was characterized by bradycardia with fall of blood pressure, inhibition of respiration, esophageal contractions (which might be independent of the laryngeal movements of deglutition), and either an increase or decrease of gastric peristalsis. The similarity of this response to that in the present human material is striking and would appear to be more than coincidence. The susceptibility of the human mesial temporal area to afterdischarge from stimulation has been noted by several authors.[18] Kaada[9] and Sloan, Pool, and Ransohoff[25] report the coincidence of afterdischarge with the interval of respiratory arrest on stimulation of this region. This observation and the finding that respiratory inhibition may long outlast the duration of the stimulus suggest that the effect of the primary stimulation may be augmented and prolonged by the initiation of a perpetuated epileptiform discharge in this area. Thus, lower areas receiving projections from the periamygdalar region may be subject to bombardment of considerable intensity and duration.

Wall and Davis[2] found that the blood pressure responses elicited from the region of the uncus in lower primates are transmitted by a descending pathway independent of the hypothalamus which passes into the lateral portion of the cerebral peduncle. This direct pathway between the mesial temporal region and the brain stem was first demonstrated anatomically in man by Zingerle,[31] and the finding was recently confirmed in further human material.[32] In sum, these facts suggest that the temporal autonomic responses have their fundamental organization at much lower levels in the brain stem, where the same functional pattern may be activated by afferent volleys from both the periphery and the rhinencephalic portions of the brain.

## SUMMARY

The orbitotemporal cortex of 11 patients undergoing pituitary surgery for the palliation of metastatic cancer was studied for autonomic responses to electrical stimulation. General anesthesia was used, and recordings were made of blood pressure, pulse rate, respiration, esophageal and gastric motility, and the pneumoplethysmogram. Responses from the posterior orbital region and the infundibulum of the hypothalamus were meager, although mechanical stimulation coincident with section of the hypophyseal stalk might yield profound changes.

An area on the anterior uncus at its junction with the hippocampal gyrus produced well-defined constant responses. The blood pressure usually fell coincident with bradycardia but might rise. Respiration was inhibited or arrested. Arrest might occur at any stage in the res-

piratory cycle. Esophageal contractions appeared which might follow or be independent of the laryngeal component of deglutition. In two instances, a well-defined increase in gastric contractions occurred. No changes were noted in the plethysmogram. The similarity of this complex of responses to that elicited by afferent stimulation of the superior laryngeal nerves and vagi in lower animals was noted and discussed.

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# Delayed postoperative hemorrhage from intracranial aneurysm after craniotomy for tumor

Patrick E. Taylor, M.D.

THE SIGNS of intracranial hemorrhage after craniotomy for brain tumor are most often of insidious onset in the first postoperative hours or days. So gradual is the usual development of this problem that frequently it is indistinguishable clinically from the picture caused by cerebral swelling. Occasionally, postoperative hemorrhage is of delayed onset and apoplectiform character, suggestive of sudden and massive bleeding from aneurysm or other primarily vascular lesion, differing in no respect from intracranial bleeding as it is encountered in its spontaneous form. While the underlying pathologic processes may be as diverse in the surgical case as in the patient upon whom no surgery has been performed, this communication will deal only with hemorrhage which may be related to the surgical procedure itself and resulting from the rupture of a preexisting unsuspected saccular arterial aneurysm or aneurysm caused by surgical trauma to intracranial vessels.

Scant reference is made in the literature to the problem of delayed apoplectiform postoperative hemorrhage from aneurysm. The author, in a search of the world literature of the last sixty-five years, was able to find only one such report.[1] The case described is especially germane to the present discussion in that there is evidence that the bleeding stemmed from an aneurysm caused by arterial trauma incident to surgical manipulation for removal of a tumor. This report is of sufficient interest to briefly summarize at this point.

The patient, a 54-year-old man, was first seen for symptoms of a right frontal space-occupying lesion. Cerebral arteriography performed preoperatively confirmed the presence of a tumor but did not demonstrate any intrinsic abnormalities of the vessels themselves. At operation, while a meningioma of the orbital roof was being removed, a small artery was torn at its origin from the middle cerebral trunk. Hemorrhage was controlled by the cautious application of clips placed so as to spare the lumen of the parent vessel. After surgery, the patient did well until the seventeenth postoperative day, when he suddenly bled intracranially after straining at stool. Repeat angiography revealed a pea-sized saccular aneurysm of the middle cerebral artery in the region of the tumor resection. Upon reexploration, the lesion was found at the site of the previous vascular injury. Treatment, consisting of clipping of the neck of the sac, was followed by recovery.

The conclusion of the author presenting the case was that the lesion was in actuality a false aneurysm, caused by the progressive dilation of the thrombus formed at the site of the incompletely sealed arterial rent. As no histologic material was examined, proof of the traumatic etiology of this aneurysm rests on the surgical evidence, which in this case seems adequate.

While the entity of surgically produced aneurysm has been mentioned in passing[2] and the possibility of such an occurrence would be denied by few neurosurgeons, the above case also constitutes the only reported instance which could be found in the literature wherein

From the Department of Surgery, University of California Medical Center, Los Angeles.

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surgical trauma has been implicated as an etiologic agent of intracranial saccular aneurysm.

With regard to the question of bleeding from preexisting lesions, the possibility of the coexistence of congenital aneurysm with the tumor seems especially pertinent, since such lesions are among the most important causes of intracranial hemorrhage in the nonsurgical case. As a preliminary consideration, it would be of some use to know the frequency of the association of these two apparently unrelated disease processes. Data on this subject have, however, not been previously reported.

Since the incidence of intracranial aneurysm of the developmental type in the general population, as estimated from the findings of various authors,[3–5] is at least 0.5%, it would appear, on the basis of chance, that such a lesion might exist in perhaps 1 of every 200 patients with tumor. At the other extreme is the impression as to the incidence of this problem gained by a search of the literature of the last three and a half decades, which resulted in the finding of only 7 cases of coexistent tumor and saccular aneurysm.[6–12] That this paucity of reported cases does not reflect the true incidence of this association is attested to by the fact that the author was able to find 5 additional unreported cases in the neurosurgical files of the Atkinson Morley's Hospital, Wimbledon, England, which were seen during a six-year period ending in 1959. In that same interval, approximately 1,500 verified primary intracranial neoplasms were diagnosed at that institution. The fact that all but 2 of these aneurysms were found on the same side as the tumor during either arteriography or surgery indicates that the actual incidence of these lesions in patients with tumor is greater

9 CASES OF ASSOCIATED ANEURYSM AND TUMOR

| *Patient* | *Aneurysm location* | *Tumor type and site* | *Presenting symptoms and signs* | *Relation of hemorrhage to surgery* | *Probable etiology of aneurysm* |
|---|---|---|---|---|---|
| D. W. C. | Right anterior cerebral at genu | Astrocytoma grade III right frontal lobe | Tumor; increased pressure | Fatal postoperative bleeding, twelfth day | Traumatic versus developmental |
| P. J. NH 13221 | Left posterior communicating and posterior cerebral; upper basilar | Meningioma left middle fossa | Tumor; increased pressure | Fatal hemorrhage on twenty-eighth postoperative day | Developmental |
| H. E. E. | Right middle cerebral bifurcation seen at surgery | Astrocytoma, grade III right frontal and temporal | Tumor; increased pressure | Fatality 48 hours postoperative ? Bleed | Developmental |
| A. S. | Right anterior cerebral proximal to anterior communicating | Pituitary adenoma | Tumor plus subarachnoid hemorrhage | Hemorrhage before surgery | Developmental |
| W. T | Bilateral middle cerebral; rupture on right | Right parasagittal meningioma | Subarachnoid hemorrhage, in coma | Hemorrhage before surgery | Developmental |
| F. R. | Right internal carotid, cavernous sinus | Astrocytoma grade III right temporal | Tumor; increased pressure | No bleeding | Developmental |
| E. H. NH 39438 | Right internal carotid at bifurcation; postoperative diagnosis confirmed | Pituitary adenoma; operation in 1931; treated with radon seeds | Sellar lesion; previous tumor surgery | No bleeding | Developmental |
| H. F. NH 38575 | Right middle cerebral bifurcation seen at surgery | Pituitary adenoma | Sellar lesion; subarachnoid hemorrhage | No surgery | Developmental |
| A. P. | Right internal carotid at level of posterior communicating | Astrocytoma grade III right frontal | Tumor; normal pressure | No bleeding | Developmental |

than the 0.33% suggested by the above figures and approaches that estimated for the general population. In addition, 3 cases were found in the pathologic files of the National Hospital, Queen Square, London, and 1 case was seen by the author himself at the Veterans Administration Hospital, Los Angeles, bringing the total of such heretofore unreported cases to 9.

The table sets out the salient features of these cases; 2 of the 9, noteworthy because of the occurrence of delayed hemorrhage from aneurysm after decompressive tumor surgery, will be outlined more fully in order to illustrate further the peculiarities of this problem.

CASE REPORT

**Case 1.** D.W.C., a 33-year-old aircraft worker, was admitted to Wadsworth General Hospital, Veterans Administration, Los Angeles, on June 25, 1955, with a three-year history of major convulsive seizures. More recently, he had developed headache, increasing weakness of the left limbs, and frequent focal motor seizures beginning in the left lower extremity. Examination revealed slightly blurred disk margins and moderate left hemiparesis. A right carotid arteriogram of good diagnostic quality demonstrated the presence of a space-occupying lesion in the right frontal region but gave no evidence of aneurysmal dilation anywhere (Fig. 1).

Fig. 1. Preoperative arteriogram. Distal part of anterior cerebral complex straightened and displaced due to tumor. No aneurysm seen

At the time of craniotomy, the dura mater was found to be under extreme pressure due to a cystic and necrotic infiltrating glioma. When resection of the right frontal pole was carried out, some difficulty was experienced with arterial and venous bleeders in the interhemispheral fissure. This was dealt with by means of silver clips.

After surgery, the patient did well until the third postoperative day, when signs of mild meningeal irritation appeared. Lumbar puncture at that time showed the presence of slightly blood-tinged cerebrospinal fluid under a pressure of 380 mm. of water. The patient's course was thereafter one of improvement until the twelfth day, when he suddenly had severe bilateral headache, vomiting, and nuchal rigidity associated with weakness of the left arm. Spinal tap on that occasion revealed grossly bloody cerebrospinal fluid and a pressure in excess of 600 mm. Repeat angiography was performed and demonstrated a saccular aneurysm of the right anterior cerebral artery distal to the anterior communicating artery, in the vicinity of a cluster of hemostatic clips (Fig. 2).

On the twenty-first day after the initial surgery, the operative site was reexplored. After

Fig. 2. Postoperative arteriogram showing saccular aneurysm on anterior cerebral artery at site of origin of frontopolar branch. Note proximity of hemostatic clips.

removal of a large blood clot from the area of the resection, an aneurysm, saccular but sessile, was found on the right anterior cerebral artery. This was situated as shown on the contrast study and was just outside the limit of the resection. Treatment consisted of trapping of the lesion between clips. Further exploration led to the discovery of intraventricular clot, which was not accessible to complete removal.

After the second operative procedure, there was no improvement in the patient's already poor condition. His course was one of slow deterioration, until he died on the twenty-seventh day after the first craniotomy.

At necropsy, there was marked swelling of the right frontal lobe. The aneurysm was found as previously mentioned and was 7.5 mm. in diameter. Extending through the white matter of the superomesial part of the frontal lobe was a necrotic, infiltrating tumor, which proved on microscopic examination to be a glioblastoma. The anterior extremity of the corpus callosum and surrounding structures had been destroyed by massive hemorrhage, which formed a complete cast of the ventricular system. Sections made of the aneurysm demonstrated a thin sac wall composed of scanty collagenous tissue and small vessels. The lumen was filled with laminated semi-organized thrombus. No endothelial layer was seen. The zone of transition betwen the parent artery and the sac wall was not available for study.

**Comment.** In this case, the anterior cerebral arteries were not observed at operation; hence, no incontrovertible evidence is available as to the etiology of the aneurysm found on postoperative angiography or subsequent reexploration. The negative preoperative contrast study suggests that the lesion developed after the initial operation. However, in view of the known failure of angiography to demonstrate existing aneurysms in every circumstance, this finding must be treated with some reserve. The pathologic evidence is of little help, although the poorly developed structure of the sac wall is not the usual finding in a ruptured aneurysm of the developmental type.

**Case 2.** P.J., a 38-year-old woman, was admitted to the National Hospital, Queen Square, London, on November 29, 1948, because of a history of fits for six years and severe headaches for three years.

Examination on admission was entirely negative except for possible early papilledema on the right and a slight hyperreflexia and questionable extensor plantar response on that side. Skull roentgenograms were suggestive of an intrasellar lesion. Left carotid arteriogram demonstrated the presence of a mass in the left middle fossa. In this study, the posterior communicating artery did not visualize and no intrinsic vascular lesion was seen.

On December 31, 1948, a left temporal craniotomy was performed, leading to the exposure of very tense dura mater and brain. The temporal lobe was elevated, exposing a soft, extremely vascular encapsulated tumor arising from the floor of the middle fossa and extending to the midline. Attempts at morcellation were not successful because of the profuse bleeding from the thin-walled vessels, so the tumor was removed by finger dissection. The resultant brisk hemorrhage from arterial channels thereby opened was controlled by the application of tantalum clips. Histopathologic examination of the tumor showed it to be a vascular meningioma.

Postoperatively, the patient had a right hemiparesis, a right homonymous hemianopsia, and marked dysphasia. These deficits were thought clinically to be due to thrombosis of the left posterior cerebral artery. Her condition was unremarkable otherwise until the twenty-eighth postoperative day, when she suddenly went into a coma and died a few hours later.

Postmortem examination demonstrated the tumor bed in the under surface of the temporal lobe to be free of residual neoplasm; 2 saccular aneurysms were found. The one at the junction of the rather small left posterior communicating artery and the posterior cerebral trunk was 5 mm. in diameter, adherent to the third nerve, and ruptured at the apex of its sac superiorly. The second aneurysm was on the upper part of the basilar artery, had not ruptured, and was 3 mm. through its sac. A tantalum clip was located so as to occlude the posterior cerebral artery proximal to the posterior communicating artery. An infarction was noted in the left occipital lobe and extended

into the internal capsule. The hemorrhage had dissected upward from the point of rupture through the anterior hypothalamus into the ventricles. Histologically, the smaller aneurysm showed an almost abrupt ending of the elastica interna in the neck of the sac. In the case of the ruptured aneurysm, only the sac was available for study. This structure consisted of a wall composed of well-developed adventitia and thickened intima.

**Comment.** Histologic examination of the two lesions revealed findings typical of aneurysms of the developmental variety. The marked intimal proliferation lining the ruptured sac points to the probable chronicity of this lesion and hence to its developmental origin. As in our first case, intracranial pressure was increased preoperatively. Craniotomy in each instance appeared to bring about marked reduction of this tension.

Aside from the possible etiologic differences, it can be seen that there are a number of striking similarities among the 3 cases summarized above. In this respect, several common features are worthy of comment:

1] None of the patients had symptoms referable to aneurysm preoperatively, the surgery being performed in each case for tumor.

2] All of the patients had angiograms negative for aneurysm before exploration and upon subsequent review. It should be mentioned, however, that, while in Case 2 the study was negative for aneurysm, the lesions were on the basilar arterial tree, no part of which was visualized.

3] Tumor resection was carried out in all 3 cases in the immediate vicinity of major arteries, and in each case there was some difficulty with hemorrhage in the neighborhood of these large cerebral vessels.

4] After surgery, the patients were apparently improving until the occurrence of massive intracranial hemorrhage, differing clinically in no way from the picture due to spontaneous hemorrhage from aneurysm of the usual presentation. While in Case 1 there is evidence that a small amount of bleeding took place within the first three days, apoplectiform hemorrhage did not supervene until the twelfth day. In the second case, twenty-eight days elapsed before the fatal ictus. In the case cited from the literature, bleeding took place on the seventeenth postoperative day.

5] Angiography was repeated in 2 of the cases in order to determine the etiology and site of the bleeding, and in both instances the lesion was shown to be a saccular aneurysm, visualized in an area where no such abnormality was seen preoperatively.

6] In the 2 patients subjected to reoperation and in the postmortem examination of the third case, a ruptured saccular aneurysm was found in the immediate area of the surgery.

7] In all 3 of these cases, moreover, the lesions were situated in the neighborhood from which the troublesome operative bleeding arose.

## DISCUSSION

While this is an analysis of but 3 cases, the combination of operative difficulty with hemorrhage in the region of large intracranial arteries and delayed, sudden, and massive intracranial hemorrhage is too suggestive to ignore. When these features occur together, the possibility of ruptured aneurysm, whether traumatic or developmental, should be considered. Although in these cases the bleeding occurred from aneurysms located adjacent to the surgical field, angiography before reexploration should, of course, be carried out in order to rule out the possibility of the bleeding lesion being elsewhere in the cranial chamber. This possibility is illustrated by the findings set forth in the table. Although the aneurysm was spatially closely associated with the tumor in 5 instances, the remaining 4 cases harbored 5 aneurysms somewhat removed from the site of the neoplasm. At reexploration, exposure of the bleeding aneurysm might have been accomplished via the original craniotomy in but 2 of these latter cases. In 2 patients, the site of the aneurysm was altogether too far from that of the tumor to be attacked through the original exposure. Indeed, in Case 5, with a right parasagittal meningioma, hemorrhage occurred preoperatively from an aneurysm of the right middle cerebral artery. A similar unruptured lesion was also present on the opposite side.

In both the presented cases, a traumatic etiology for these aneurysms must be considered in view of the proximity of the tumor

removal and the known vascular manipulation. However, in contrast to the case cited from the literature, no direct evidence can be offered against the possibility that these aneurysms existed before surgery. In Case 1, positive evidence for a surgical origin hangs on the slender thread of negative preoperative angiography. Such histologic material as is available is inconclusive, although the structure of the sac wall, with its scanty adventitia, suggests the possibility of this lesion being a false aneurysm and hence traumatic. Examination of the junction of the sac with the parent vessel might have enabled a definite diagnosis. In Case 2, the presence of 2 aneurysms, both histologically compatible with a preexisting pathology, is against a surgical etiology.

The question concerning the histopathologic differentiation of traumatic from congenital intracranial saccular aneurysm is one that has never been satisfactorily resolved with regard to those lesions possibly due to either surgery or head injury. In the case of the latter problem, numerous cases have been reported. Proof in most of those cases seems to have been based mainly on circumstantial evidence. In cases where the material is more convincing,[13,14] final proof is lacking because of the dearth of clearcut and undisputed criteria for the differentiation of this sort of aneurysm from that of the developmental type. In view of this, it would seem unsafe to diagnose aneurysm secondary to surgical trauma unless positive evidence is at hand as to the status of the artery in question at the time of operation, thereby excluding a preexisting lesion.

As it seems more probable that the aneurysms in Case 2 were of the developmental type, some consideration should be given to the possible role of intracranial surgery in precipitating hemorrhage from such an aneurysm. As with massive intracranial bleeding after lumbar puncture, laminectomy, and other procedures, the possibility of coincidence cannot be ruled out, since bleeding of identical sort is so frequent without the presence of such factors. Since, however, it must be conceded that surgery might have a precipitating influence, some speculation as to its mechanism is in order.

It is logical to assume that the rate of aneurysmal dilation, and its predisposition to bleed, is partially a function of the intraaneurysmal pressure on the one hand and of the resistance to this influence by the sac wall and by what support is contributed by the surrounding tissues and the cerebrospinal fluid pressure on the other. From this it can be seen that any circumstance that decreases the resistance of the aneurysm to the onslaught of the blood pressure by injuring the sac wall or by decreasing the tension of the adjacent tissues and fluids may favor further dilation and perhaps earlier rupture. In cases of tumor with chronically increased intracranial pressure, the tendency to dilation on the part of the aneurysm may be checked, at least for a time. Operative decompression and tumor removal may have the effect of decompensating this delicate balance, not only by disruption of the sac locally but also by radically decreasing the surrounding tissue and fluid pressure.

While these assumptions may well constitute an oversimplification of the pathogenesis of aneurysmal rupture in such cases, some support is lent them by the circumstances of certain of these cases. Of 4 patients cited in the table presenting with the signs of intracranial tumor and increased pressure and in whom no previous bleeding had occurred, 2 died as the result of postoperative hemorrhage from ruptured saccular aneurysm. In addition, a third patient, in whom the aneurysm was seen at surgery, died a few hours after suddenly going into coma on the second postoperative day. Although no postmortem examination was performed, the mode of exitus strongly suggests that ruptured aneurysm was the cause of death.

## SUMMARY AND CONCLUSIONS

Intracranial hemorrhage of apoplectiform type due to ruptured arterial aneurysm and of delayed onset after surgery for intracranial tumor is rarely reported, 1 case being found in the world literature of the last sixty-five years. This case, one of aneurysm secondary to surgical trauma, and 2 previously unreported instances of postoperative aneurysmal bleeding present several striking similarities, which, despite etiologic differences, might be taken as being characteristic of this problem. In all 3 cases, tumor removal was marked by difficulty with bleeding vessels in the region

of the subsequently discovered ruptured aneurysm. In each case, the patient was improving postoperatively when massive bleeding took place, on the twelfth, seventeenth, and twenty-eighth days, respectively. A fourth patient, with aneurysm seen at surgery, died after suddenly going into coma on the second day after operation, presumably with ruptured aneurysm.

The coexistence of preexisting intracranial saccular aneurysm in cases of primary intracranial neoplasm is not as rare as the literature would indicate, since the author was able to find a total of 9 such previously unreported cases. Of these, 5 were seen in a series of 1,500 neoplasms. The figure of 0.33% for the incidence of aneurysm in cases of brain tumor derived from this data is probably low.

Since positive histopathologic criteria upon which to base a diagnosis of traumatic saccular aneurysm do not exist except in theory, a definite diagnosis of aneurysm secondary to surgery cannot be reasonably made without clear evidence that no such aneurysm existed until after operation.

It is suggested that decompressive tumor surgery may accelerate some of the pathologic processes involved in aneurysmal dilation, thereby bringing about early hemorrhage from a preexisting lesion.

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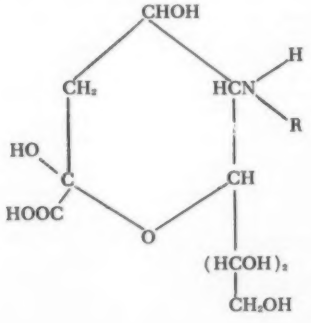
# Identification and quantitation of *N*-acetylneuraminic acid in human cerebrospinal fluid

Ruth Kerr Jakoby, M.D., and Leonard Warren, M.D., Ph.D.

SEVERAL YEARS AGO it was recognized that sialic acids, which are widely distributed among the vertebrates[1,2] and are found in some bacteria,[3] were present in brain and more specifically in its gangliosides[4,5] and lipomucoproteins.[6] Since cerebrospinal fluid (CSF) is readily obtainable and applicable in clinically useful tests, it was hoped that its sialic acid content might be a sensitive index of normal and abnormal physiology of the central nervous system.




Neuraminic Acid R = H

N-Acetylneuraminic Acid $R = CH_3C(=O)-$

Although studies on the concentration of the sialic acids in CSF have been reported, the assay methods which were employed were nonspecific and have engendered controversy because interfering factors were not eliminated. A preliminary study with the thiobarbituric acid assay method for sialic acids indicated that the concentration of these compounds in CSF was considerably less than that reported in the literature.[7] Employing this relatively sensitive and specific procedure, the free, bound, and total sialic acids may be determined. The present communication presents the results of a survey of the free and bound sialic acids in the CSF of 170 patients. The sialic acid present in CSF has been identified as *N*-acetylneuraminic acid (NANA), which is distributed in a free form as well as bound to both large, nondialyzable and small, dialyzable molecules.

## MATERIALS

Samples of CSF were obtained largely from the pathology laboratories of the District of Columbia General Hospital; several specimens were contributed by Walter Reed Army Medical Center, St. Elizabeths Hospitals, and the George Washington University Hospital. CSF was refrigerated upon receipt. Samples were coded and assayed without reference to name or disease state. Fluids which were contaminated with gross blood or cells and those which were xanthochromic were discarded.

## ASSAY SYSTEM

Since the thiobarbituric acid assay measures only unbound sialic acids, values for total CSF sialic acid concentration were obtained after hydrolysis of the specimen. Each sample of CSF (0.4 cc. to which was added 0.05 cc. of 1 *N* $H_2SO_4$) was hydrolyzed for one hour at 80° C. to release bound sialic acids.

From the Neurosurgery Service, District of Columbia General Hospital, and George Washington University Hospital, Washington, D.C., and National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md.

Sialic acids were determined on 0.4 cc. aliquots of the hydrolyzed and also unhydrolyzed samples of CSF in the following manner:[7] To the aliquot, 0.1 cc. of 0.2 *M* sodium metaperiodate in 9 *M* phosphoric acid was added. After reacting for twenty minutes at room temperature, 1.0 cc. of sodium arsenite (10%) in a solution of 0.5 *M* sodium sulfate was added and the tubes shaken and allowed to stand for five minutes until all of the brown color was discharged. To each tube was added 3 cc. of an 0.6% solution of thiobarbituric acid* in 0.5 *M* sodium sulfate solution. The tubes were shaken and then placed in a vigorously boiling water bath for fifteen minutes. After cooling in tap water for five minutes, an equal volume of cyclohexanone was added. The tubes were shaken vigorously twice and then centrifuged in a clinical centrifuge.

Optical densities of the top, clear, organic phase were determined at 532 and 549 m$\mu$, and correction was made for material in CSF which produces a chromogen with a maximum absorption at 532 m$\mu$. This is the major chromogen formed in the thiobarbituric acid reaction which seriously interferes with the quantitation of sialic acids. In order to correct for the interfering chromogen, the ratio of the observed optical densities at 549 m$\mu$ over that at 532 m$\mu$ was determined, and the correction constant, C, was obtained from Figure 1. This value C, the molecular extinction coefficient,[7] and the observed optical density at 549 m$\mu$ ($OD_{549}$) were inserted into the following equations:

$$\text{Total sialic acid (mg.\%)} = OD_{549} \times C \times \frac{\text{Volume}}{\varepsilon} \times (\text{M.W. of NANA}) \times \frac{100}{0.40}$$

$$= OD_{549} \times C \times \frac{4.55}{57000} \times 309 \times \frac{100}{0.4}$$

$$= 6.17 \times OD_{549} \times C$$

$$\text{Free sialic acid (mg.\%)} = OD_{549} \times C \times \frac{4.50}{57000} \times 309 \times \frac{100}{0.4}$$

$$= 6.10 \times OD_{549} \times C$$

*Several commercial preparations of "2-thiobarbituric acid" are really the disodium salt of this acid. The latter is far more soluble than the acid in water. Either may be employed in the assay; the free acid was used here.

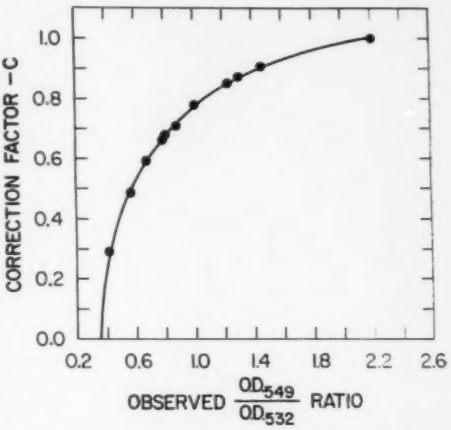



Fig. 1. Determination of correction factor C. Correction is for substances such as 2-desoxyribose, which produce a chromogen with an absorption maximum at 532 m$\mu$ in the thiobarbituric acid reaction.[8] Curve is calculated from the observed molecular extinction coefficients of NANA and 2-desoxyribose, both at 532 and 549 m$\mu$.

$$\frac{OD_{549}}{OD_{532}} \text{ ratio} = \frac{(\text{NANA})(\varepsilon_2) + (\text{desoxyribose})(\varepsilon_4)}{(\text{NANA})(\varepsilon_1) + (\text{desoxyribose})(\varepsilon_3)}$$

$$C = 1 - \left( (\text{desoxyribose}) \frac{\varepsilon_4}{\varepsilon_2} \right)$$

Where $\varepsilon_1$ is the molecular extinction coefficient $\times 10^{-3}$ of NANA at 532 m$\mu$ = 26; where $\varepsilon_2$ is the molecular extinction coefficient $\times 10^{-3}$ of NANA at 549 m$\mu$ = 57; where $\varepsilon_3$ is the molecular extinction coefficient $\times 10^{-3}$ of 2-desoxyribose at 532 m$\mu$ = 133; and where $\varepsilon_4$ is the molecular extinction coefficient $\times 10^{-3}$ of 2-desoxyribose at 549 m$\mu$ = 48. Points on the curve were derived experimentally from known mixtures of NANA and 2-desoxyribose.

The correction was less than 12% in the determination of total sialic acids and less than 22% for free sialic acids. Previous studies have shown that values for the sialic acid content of tissues can be obtained by this method which are in good agreement with values obtained by the anion exchange resin method.[9] Authentic NANA isolated from human blood proteins[10,11] served as a standard in the assays.

Figure 2 illustrates the release of sialic acids from CSF under the hydrolytic conditions used. From the curve, it is evident that routine hydrolysis of CSF for one hour is satisfactory. Negligible destruction of NANA occurs during hydrolysis in the presence and in the absence of CSF.

The following experiment indicates that reliable estimates of sialic acids in CSF can be made using 0.8 cc. of CSF, 0.4 cc. for free and 0.4 cc. for total sialic acids. The levels of free and total sialic acids were determined in 17 samples of CSF using 0.1, 0.2, 0.3, and 0.4 cc. aliquots of hydrolyzed and unhydrolyzed fluid. The mean of the values determined from a slope was 1.62 mg.% for total sialic acids and 0.44 mg.% for free sialic acids. The corresponding figures calculated from the optical densities of the 0.4 cc. aliquot were 1.60 and 0.43 mg.%. The mean of the differences between the total sialic acid values determined by the 2 methods was 0.10 and that for the free sialic values was 0.04.

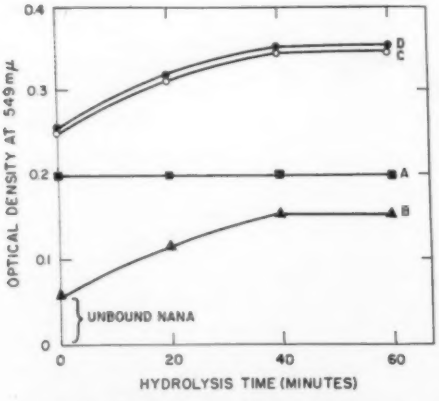



Fig. 2. Three series of tubes, 4 in each series, were made up. In the first series, each tube contained 0.016 μmole of NANA, curve A; the second series contained 0.35 cc. of CSF, curve B; and the third series contained both NANA and CSF, curve C. The final volume in each tube was 0.4 cc., with a final concentration of 0.1 *N* $H_2SO_4$. The tubes were heated at 80° C. for thirty, forty-five, and sixty minutes and then assayed by the thiobarbituric acid assay. Curve D was obtained by adding the optical density values of curves A and B.

No detectable loss of sialic acids occurs during storage of CSF at −14° C. Several determinations for free and total sialic acids were carried out on 3 specimens of CSF over the course of a month. The standard deviations for sialic acid values for each of the 3 samples based on 6 determinations for each sample were 0.07, 0.04, and 0.06 mg.% for free sialic acid and 0.12, 0.02, and 0.09 mg.% for the bound form. This not only demonstrates that samples of CSF can be safely stored without deterioration of sialic acid but is also to be taken as evidence for the reproducibility of the method employed. A fourth sample of CSF was assayed within one hour after removal from a patient and subsequently frozen and assayed 2 more times. No significant drop in sialic acid concentration was found upon storage.

Since the orcinol reaction has been the most commonly used procedure for the determination of the sialic acid level of CSF, it was of interest to compare the results obtained by this method with those of the thiobarbituric acid assay. The values obtained by the orcinol method[12] were two- to threefold greater than those from the thiobarbituric acid assay. Thus, 4 samples of CSF were found to contain 3.52, 3.12, 3.34, and 3.33 mg.%, respectively, employing the orcinol method, while 1.79, 1.04, 1.47, and 1.43 mg.%, respectively, were obtained for the same samples with the thiobarbituric acid assay.

### INDENTIFICATION OF *N*-ACETYLNEURAMINIC ACID

NANA was isolated from 500 cc. of pooled CSF. The CSF was concentrated to 25 cc. on a rotary evaporator and then dialyzed against 900 cc. of distilled water at 4° C. for twenty-four hours. The dialysis fluid was evaporated to dryness, the solids extracted with 2.5 cc. 80% ethanol, the ethanol removed *in vacuo*, and the aqueous solution placed on a column of Dowex-1 formate (0.8 x 5 cm.). NANA was eluted with 0.6 *N* formic acid.

Bound NANA was hydrolyzed by adding 0.25 cc. of 10 *N* $H_2SO_4$ to the 25 cc. of concentrated, dialyzed CSF and heating for one hour at 80° C. After neutralizing with saturated barium hydroxide solution, the heavy precipitate was removed by centrifugation. The

precipitate was washed twice with cold distilled water, and the combined supernatant solution and water washes were evaporated to dryness and purified on a column of Dowex-1 formate, as noted previously. Both bound and free material from the column reacted in a fashion characteristic of sialic acids in the Ehrlich,[12] orcinol,[12] and diphenylamine[13] tests. These substances were readily adsorbed by Norit-A and eluted with 50% methanol.[14]

Both bound and free materials were chromatographed on Whatman No. 1 paper (ascending), employing 2 solvent systems* which separate *N*-acetylneuraminic acid from *N*-glycolylneuraminic acid. The position of these compounds on paper was detected with a thiobarbituric acid spray reagent.[16] The materials isolated from CSF were chromatographed separately as well as together with *N*-glycolylneuraminic acid and NANA. Both free and bound sialic acid was found to co-chromatograph with NANA; no *N*-glycolylneuraminic acid was found.

In one experiment, 92% of bound NANA was released by sialidase of *Vibrio cholerae*, as determined by the thiobarbituric acid assay.

Although free NANA accounts for approximately 35% of the total, several workers have shown that about 60 to 80% of the NANA of CSF is dialyzable or nonprecipitable by trichloroacetic acid or ethanol,[17–20] that is, it is not bound to large molecules, such as mucoproteins. This may now be explained by the finding that much of the NANA of CSF which is dialyzable is not free but is bound to small molecules and, therefore, not reactive in the thiobarbituric acid assay. When the dialysis fluid is treated with a sialidase (neuraminidase) from cholera or is heated at 80° C. for one hour in 0.1 *N* $H_2SO_4$, free sialic acid is released. Thus, sialic acid of CSF may be bound not only to proteins but also to smaller, dialyzable compounds, perhaps analogous to neuramin-lactose. Preliminary calculation indicates that approximately equal parts of CSF and NANA are free and bound to large and to small elements. Studies on bound, dialyzable sialic acid containing compounds which are not precipitated by ethanol or phosphotungstic acid will be reported in a separate communication.

*Solvent 1,[15] n-butanol: n-propanol: 0.1 *N* HCl, 1:2:1. Solvent 2, ethanol: water: ammonia, 80:20:1. NANA has an RF or 0.30 in solvent 1 and 0.35 in solvent 2. *N*-glycolylneuraminic acid has an RF of 0.20 in solvent 1 and 0.27 in solvent 2.

TABLE 1
SUMMARY OF NANA CONTENT IN SELECTED CATEGORIES

| *Number of patients* | *Diagnosis* | *NANA (mg. per 100 cc.)** *Free* | *Total* |
|---|---|---|---|
| 57 | Control group | 0.42±0.14 | 1.16±0.52 |
| 5 | Neoplasm, nonneurologic | 0.45±0. 7 | 1.29±0.28 |
| 8 | Meningitis | 0.33±0.22 | 2.63±0.76 |
| 7 | Alcoholism without seizures | 0.46±0.30 | 1.15±0.80 |
| 10 | Alcoholism with seizures | 0.54±0.28 | 1.38±0.45 |
| 11 | Seizures without alcoholism | 0.37±0.10 | 1.04±0.26 |
| 27 | Cerebrovascular accident | 0.51±0.13 | 1.57±0.60 |
| 13 | Syphilis | 0.42±0.14 | 1.16±0.45 |
| 5 | CNS syphilis | 0.37±0.04 | 1.14±0.60 |
| 6 | Herniated disk | 0.39±0.18 | 1.41±0.45 |
| 8 | Hypertension | 0.43±0.60 | 1.33±0.45 |
| 5 | Pneumonia | 0.37±0.11 | 1.00±0.75 |

*±Standard deviation

CONCENTRATION IN CSF

Since normal individuals were not included in this survey, patients admitted with a variety of nonneurologic diseases have been included in the control group. It is obvious that, even with these patients, sufficient suspicion of neurologic involvement existed to indicate the performance of a lumbar puncture.

**Control Group.** Included in this category were all patients other than those with neurologic or psychiatric involvement. The average concentration for this entire group of 57 patients, varying in age from 6 to 86 years, was $0.42 \pm 0.14$ and $1.16 \pm 0.52$ mg. per 100 cc. for free and total NANA, respectively (Table 1). The relatively high standard deviation is indicative of the large variation in concentration which is observed. Similarly high variations were obtained when viewing the results within single disease groups (Table 1). Included in the control group and not listed elsewhere in Table 1 were CSF obtained from patients with the following disease states: amyloidosis, barbiturate intoxication, burns, cephalohematoma, diabetes, goiter, heat

prostration, labyrinthitis, miliary tuberculosis (without neurologic involvement), narcotic addiction, perineal abscess, pulmonary embolism, rheumatoid arthritis, sarcoidosis, and uremia. The neoplasm group included lymphoblastoma; multiple myeloma; and lung, breast, and pancreatic carcinoma. Other categories in which a substantial number of individuals were involved are also summarized in Table 1.

The possibility that the concentration of NANA is a reflection of protein concentration[21] does not appear to obtain in the present series. Thus, high values for both free and total concentrations are obtained with low CSF protein and vice versa. A patient with complete block due to Pott's disease, diagnosis of which was established by myelography, a positive Queckenstedt response, and by surgery had the highest protein (735 mg. per 100 cc.) and NANA (9.25 mg. per 100 cc.) concentrations of any of the cases examined. Of particular interest here is that the free NANA was 0.24 mg. per 100 cc., a finding well within the normal range. The CSF of a patient with a lumbar herniated intravertebral disk was found to contain 100 mg.% protein and 0.37 mg.% free and 1.13 mg.% bound NANA. Corresponding figures for a patient with gastroenteritis were 37, 0.44, and 2.05 mg.%, respectively.

**Psychiatric group.** The results from 12 patients with psychiatric disorders are summarized in Table 2. Included are 3 cases of schizophrenia, which are of interest because of a previous report suggesting a decrease in sialic acid concentration in this disease.[22] Average values for this series were $0.48 \pm 0.22$ and $1.24 \pm 0.44$ mg. per 100 cc. for the free and total NANA concentrations, respectively.

TABLE 2
PSYCHIATRIC GROUP

| | *NANA (mg. per 100 cc.)* | |
|---|---|---|
| | *Free* | *Total* |
| Schizophrenia | 0.92 | 2.08 |
| Schizophrenia | 0.27 | 0.99 |
| Schizophrenia | 0.63 | 1.87 |
| Senile dementia | 0.36 | 1.69 |
| Senile dementia | 0.50 | 1.37 |
| Anxiety reaction | 0.28 | 0.92 |
| Anxiety reaction | 0.37 | 1.24 |
| Mental deficiency | 0.37 | 0.64 |
| Observation, criminal | 0.33 | 0.99 |
| Neurosis | 0.90 | 1.02 |
| Conversion reaction | 0.40 | 0.88 |
| Functional headache | 0.39 | 1.19 |

**Neurologic group.** A wide variety of patients manifesting neurologic lesions have been examined, since it was among this group that alteration in the concentration of NANA might be expected. The average values for this series of 99 patients were $0.39 \pm 0.34$ and $1.69 \pm 0.95$ mg. per 100 cc. for free and total NANA, respectively. Included are patients with central nervous system syphilis, herniated intravertebral disk, cerebrovascular accident, seizures, and meningitis (Table 1) and a group of cases which include tumor, trauma, and toxic and degenerative neurologic manifestations (Table 3). Of these, only meningitis (average $0.43 \pm 0.19$ and $2.14 \pm 0.83$ mg. per 100 cc. for free and bound, respectively) and a case of complete spinal fluid block resulted in significant increase in NANA.

Comparison has been made between alcoholism, alcoholism accompanied by seizures, and seizure disorders without a history of alcoholism (Table 1); no significant differences were found. Similar considerations apply to syphilis with and without central nervous system involvement (Table 1).

## DISCUSSION

Within the limits imposed by the number and type of patients available for this study, the reported results indicate that the NANA concentration of CSF is not a useful indicator of pathology. In part, the lack of correlation of NANA levels with disease is due to the large variation in concentration which is encountered. That this variation is not a function of the precision of the assay or of protein concentration of the CSF is documented here. Of the various categories examined, only patients with meningitis or with a complete CSF block were found to have elevated NANA levels.

It has been demonstrated with the thiobarbituric acid reagent that the average value for total sialic acid is $1.16 \pm 0.52$ mg. per 100 cc. of CSF. Results with the orcinol method as used by Uzman and his coworkers,[18] who

TABLE 3

NEUROLOGIC GROUP

| Diagnosis | NANA (mg. per 100 cc.) Free | Total |
|---|---|---|
| Complete block, thoracic spine* | 0.42 | 3.67 |
| Complete block, thoracic spine* | 0.24 | 9.25 |
| Arteriovenous anomaly* | 0.05 | 0.63 |
| Subdural hematoma* | 0.37 | 0.98 |
| Subdural hematoma* | 0.27 | 0.99 |
| Subdural hematoma* | 0.40 | 0.98 |
| Meningioma* | 0.40 | 1.50 |
| Pseudohypertrophic muscular dystrophy | 0.20 | 1.01 |
| Primary lateral sclerosis | 0.18 | 0.86 |
| Hydrocephalus, postmeningitic | 0.37 | 0.71 |
| Bell's palsy | 0.23 | 0.84 |
| Pseudotumor cerebri | 0.25 | 0.76 |
| Optic atrophy | 0.66 | 1.58 |
| Multiple sclerosis | 0.33 | 1.27 |
| Multiple sclerosis | 0.36 | 1.02 |
| Incontinentia pigmenti | 0.64 | 1.21 |
| Tuberous sclerosis | 0.40 | 1.21 |
| Cerebral palsy | 0.32 | 0.56 |
| Poliomyelitis | 0.29 | 1.30 |
| Menière's disease | 0.36 | 1.29 |
| Internal carotid insufficiency | 0.32 | 0.88 |
| Charcot-Marie-Tooth syndrome | 0.57 | 1.29 |
| Cerebral atrophy | 0.32 | 1.02 |
| Cerebral atrophy | 0.36 | 1.38 |
| Cerebral atrophy | 0.29 | 1.26 |
| Peripheral neuropathy | 0.29 | 1.23 |
| Peripheral neuropathy | 0.37 | 1.19 |
| Peripheral neuropathy | 0.28 | 0.86 |
| Encephalomalacia | 0.29 | 0.78 |
| Serum sickness (aseptic meningitis) | 0.92 | 1.50 |
| Acute brain syndrome | 0.59 | 1.39 |
| Acute brain syndrome | 0.54 | 1.29 |
| Arteriosclerotic cerebrovascular disease | 0.39 | 1.79 |
| Arteriosclerotic cerebrovascular disease | 0.23 | 1.12 |

*Prior to surgery

corrected for interference by glucose, and by Papadopoulos and Hess,[23] who corrected for interference by glucose and fructose, are only slightly higher; separate assays for glucose and fructose were performed. However, values of 2.4[24] and 2.7[1] mg.% for protein-bound sialic acids and 5.1 mg.%[20] for total sialic acid have been reported. In 1 study, the mean level of sialic acids in the CSF of adults from a general hospital population was 5.38 mg.%.[22] This last group of high concentrations is most probably due to the lack of specificity of the assay coupled with failure to correct for interfering materials.

The neuraminic acid in human CSF has been identified as *N*-acetylneuraminic acid. Forms of sialic acid other than NANA are absent or, if present at all, are in very low concentration.

The data in this communication indicate that about 35% of the NANA in CSF is free and that the remainder is bound. Preliminary work indicates that approximately half of the bound form is dialyzable, that is, joined to a relatively small molecule, while the remainder is presumed to be associated with mucoprotein. Whatever the physiologic role played by the low levels of the neuramidase recently found in human and bovine serum fractions,[25] the absolute concentrations of both free and bound NANA in CSF do not appear to change during storage.

## SUMMARY

1. The concentrations of free and total sialic acid have been determined in 170 specimens of human CSF by the thiobarbituric acid assay. Concentrations reported are considerably lower than those found in the literature.

2. In the present series, few meaningful correlations between sialic acid level of the CSF and disease state could be made. Significantly high values were found only in the presence of complete spinal fluid block or meningitis.

3. NANA is the form of both the free and the bound sialic acid of human CSF.

4. The nature of free and bound NANA of CSF is discussed.

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# Histopathology of the Bing-Neel syndrome

Robert Edgar, M.D., and Thomas F. Dutcher, M.D.

THIS REPORT describes the histopathologic features of a case of Bing-Neel syndrome—macroglobulinemia with central nervous system symptoms. The discussion compares the lesions present in this case with those previously described in examples of Bing-Neel syndrome and mentions the possibility of a relationship between this and certain other cases reported as reticulum cell sarcoma of the brain or microgliomatosis. This case has been reported in some detail[1] as 1 of 3 cases of macroglobulinemia. However, the morphologic similarity to, and the possible relationship with, reticulum cell sarcoma of the brain and microgliomatosis was not emphasized. Therefore, we felt that the case should be reported separately.

## REVIEW OF LITERATURE

In 1936, Bing and Neel[2] reported 2 patients with a syndrome of hyperglobulinemia and the central nervous system symptoms of paresthesias, headache, vomiting, and paralysis. At autopsy, the brain, brain stem, and spinal cord contained areas of perivascular infiltrates composed of plasma cells and lymphocytes, proliferation of perivascular glial tissue, and neuronal degeneration. These changes were ascribed to a "toxi-infectious affection of the central nervous system." In 1937, Bing, Fog, and Neel[3] presented a third case in which there were perivascular infiltrates of plasma cells and lymphocytes in the brain, spinal cord, kidneys, skeletal muscle, and myocardium. The fourth case was reported by Wuhrmann and Wunderly[4] in 1947. Their patient had psychiatric symptoms, paresthesias, and reflex changes. Histologic findings were not reported.

The fifth case was reported by Bichel, Bing, and Harboe[5] in 1950. This patient had severe epistaxis in 1936 and, from then until his death in 1947, had progressive central nervous system symptoms of vertigo, decreased vision, decreased hearing, and left hemiplegia. At autopsy, there were massive perivascular infiltrates composed of lymphocytes and plasma cells in the brain and spinal cord, and similar infiltrates were found in the lymph nodes, spleen, bone marrow, liver, kidneys, and other organs. The anatomic diagnosis was "either chronic lymphocytic leukemia or chronic infection by an unknown agent." Ultracentrifugation of the patient's serum revealed that the hyperglobulinemia was due to increased amounts of serum macroglobulins.

Since 1950, the Bing-Neel syndrome—macroglobulinemia with central nervous symptoms—has been reported in only 4 or 5 patients, making a total of about 10 patients with this syndrome.[1,6–8]

## CASE PRESENTATION

This 60-year-old, right-handed, Italian woman was in good health until May 1956, when she noticed "cloudy vision." Her visual acuity gradually decreased, and ophthalmologic examination several months later revealed cloudy vitreous bodies in both eyes and a small area of chorioretinitis in the right eye. In November 1956, a tuberculin skin test was positive and extensive antituberculous medication was given. Subsequently, Meticorten and ACTH were given, but no visual improvement resulted. The visual acuity, initially 20/40 in both eyes, decreased to 20/200 in the left eye by March 1957.

In May 1957, she was admitted to the Clinical Center for further evaluation and possible therapy. She complained of cloudy vision, vertex headaches, mental depression of one year's duration (thought to be related to

From the Surgical Neurology Branch, National Institute of Neurological Diseases and Blindness, and the Pathologic Anatomy Branch, National Cancer Institute, Bethesda, Md.

Dr. Edgar's present address is the Department of Neurology, College of Medicine, State University of Iowa, Iowa City.

a relative's suicide), anorexia, and intermittent hematuria. Physical examination revealed diminished visual acuity, corneal keratitic precipitates, and granular precipitates, with cellular debris and opacities in the anterior and posterior chambers bilaterally. Chorioretinitis was present in the right fundus, and vitreous opacities obscured the left fundus. Other physical findings included hepatomegaly, splenomegaly, and brawny edema of the ankles. No lymphadenopathy was noted. The neurologic examination was within normal limits.

Laboratory studies revealed a hemoglobin of 12.5 gm. per cent, a white cell count of 5,800 per cubic millimeter with 37% polymorphonuclears and 55% lymphocytes, a platelet count of 172,000 per cubic millimeter, and an erythrocyte sedimentation rate of 89 mm. in one hour. The urine was normal. The total serum proteins were 6.4 gm. per cent with 2.9 gm. per cent albumin and 3.5 gm. per cent globulin. The diagnosis of Waldenström's macroglobulinemia was established by ultracentrifugation of the serum. This showed that a macroglobulin with a sedimentation rate of 18S comprised 15% of the total serum proteins. Cryoglobulins were not demonstrable. Dilution of the serum in distilled water (Sia test) produced a heavy white flocculus. Liver function tests, except for a thymol turbidity of 17 units, were normal.

Skull roentgenograms were normal. Skeletal films showed calcified hilar nodes and generalized hypertrophic osteoarthritis. No osteolytic lesions characteristic of multiple myeloma were found.

On July 12, 1957, she began to experience continuous bifrontal headaches and daily vomiting. Electroencephalograms on July 17 revealed a diffuse dysrhythmia compatible with increased intracranial pressure. A focal delta pattern over the left occipitoparietotemporal area suggested a neoplasm, and radioactive serum albumin scanning revealed an increased uptake in the same area. Neurosurgical consultation was requested, and examination revealed right hemiparesis, hyperreflexia, Babinski sign, and aphasia. Evaluation of papilledema was inaccurate due to the vitreous opacities. The patient became progressively lethargic and confused, and the aphasia, right hemiparesis, and reflex changes became more pronounced.

A ventricular tap and needle aspiration was carried out on July 25. The ventriculogram showed a massive shift to the right secondary to a large lesion in the left occipitoparietotemporal area. The ventricular fluid pressure was elevated, and the ventricular fluid protein was 29 mg. per cent. Microscopic examination of the aspirated material was suggestive of an anaplastic carcinoma.

The patient became comatose, and hypertension, bradycardia, and stertorous respirations developed. Suddenly, on August 1, 1957,

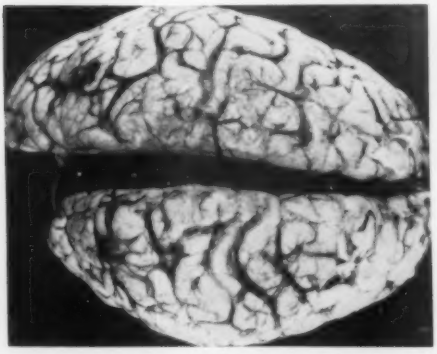

Fig. 1. Dorsal aspect of brain. Left cerebral enlargement with flattening of the gyri is seen.

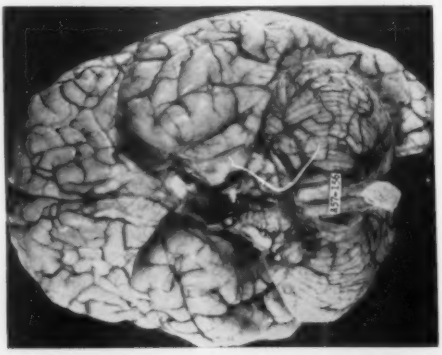

Fig. 2. Basal aspect of brain. Left uncal herniation with displacement of brain stem to right is seen.

marked hypertension occurred and respirations ceased. This terminal episode was thought to be due to a transtentorial uncal herniation.

PATHOLOGIC FINDINGS

**Gross.** The brain weighed 1,400 gm. after fixation. The left cerebral hemisphere was enlarged, and the gyri were markedly flattened (Fig. 1). Left uncal herniation was found with compression of the midbrain and pons and displacement of the brain stem to the right (Fig. 2). The midbasilar aspect of the left temporal lobe was bulging, and a friable tumor had eroded through the cortex.

On multiple coronal sections, a glistening, poorly demarcated, yellow-gray tumor replaced most of the left temporal lobe and extended into the parietal and occipital lobes. This tumor was fusiform and tapered anteriorly to the level of the optic chiasma and posteriorly to within 1 cm. of the occipital pole. The temporal and occipital horns of the left lateral ventricle at the level of the trigone were obliterated by the tumor (Fig. 3). Hemorrhage was seen in association with the needle tracts of the surgical aspiration. There was a 1-cm. globular tumor underlying the right frontal cortex bordering the median longitudinal fissure This appeared grossly similar to the tumor in the left cerebral hemisphere.

Other pertinent findings were limited to the reticuloendothelial system. The liver weighed 2,600 gm., and the hepatic lobular pattern was accentuated. The spleen weighed 720 gm., and the lymphoid follicles were prominent. The abdominal lymph nodes were enlarged, gray-white, and firm. The lymph nodes in other regions were not enlarged. No bone marrow lesions suggestive of multiple myeloma were found. Except for a few cutaneous ecchymoses at venipuncture sites, there were no hemorrhages.

**Microscopic: central nervous system.** The Virchow-Robin spaces of most of the vessels in the cerebrum, cerebellum, and brain stem were filled by a cellular infiltrate. This resembled an inflammatory infiltrate and was composed of small lymphocytes, plasma cells, a few lymphoid plasma cells, and an occasional abnormal reticulum cell (Fig. 4). The lymphoid plasma cells had a nuclear chromatin pattern like that of a lymphocyte, but the

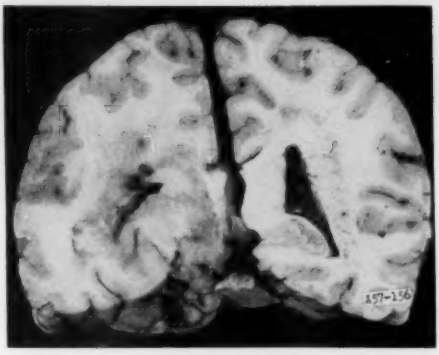

Fig. 3. Coronal section of brain. Compression of left lateral ventricle by a glistening, granular tumor is seen. Note also compression of brain stem by left temporal lobe.

nucleus was located eccentrically in a full cytoplasm with a paranuclear clear area like that of a plasma cell. Several cells of this type contained intranuclear periodic acid–Schiff (PAS) positive material (Fig. 5).

Most of the Virchow-Robin spaces which contained this cellular infiltrate were surrounded by abnormal reticulum cells. These had an irregular or deeply cleft nuclear outline,

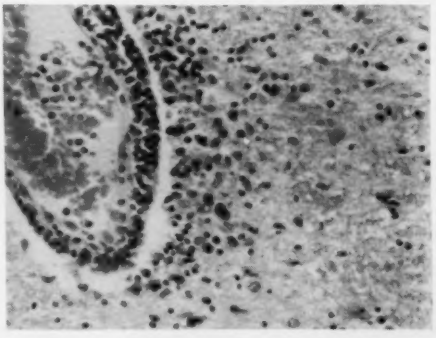

Fig. 4. Cerebral vessel. Within Virchow-Robin space is an infiltrate composed of lymphocytes, plasma cells, and lymphoid plasma cells. Note resemblance to an inflammatory infiltrate. In brain, along Virchow-Robin space, is an infiltrate of abnormal reticulum cells, lymphocytes, and plasma cells. Hematoxylin and eosin stain. × 325

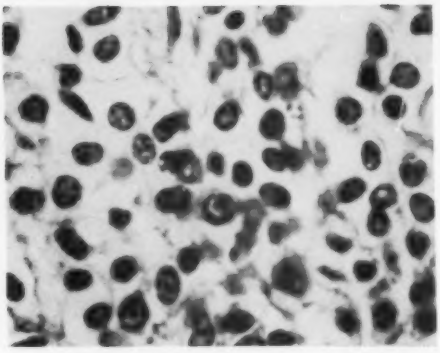

Fig. 5. Lymphoid plasma cell with PAS-positive intranuclear material which appears as a light gray area within the nucleus. Periodic acid–Schiff stain with green filter. × 1,700

and mitoses and multinucleated forms were frequent. The nuclear chromatin was finely dispersed, and there were 1 to 4 large amphophilic nucleoli. The cytoplasm was scanty to moderate in amount, and the cytoplasmic border was frequently indistinct (Fig. 6). Occasionally, there were short cytoplasmic processes joining one cell with others. A few binucleate cells with large nucleoli superficially resembled the Reed-Sternberg cells of Hodgkin's disease, but the nucleoli were not as prominent nor as eosinophilic as they are in a typical Reed-Sternberg cell. These cells

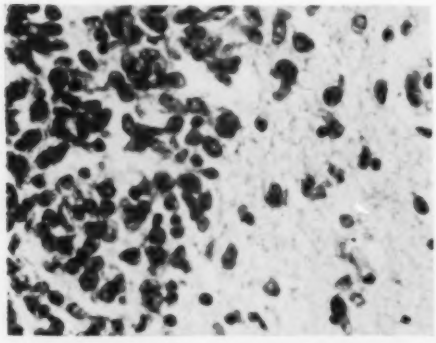

Fig. 6. Left cerebrum. Abnormal reticulum cells invading brain at periphery of tumor. Hematoxylin and eosin stain. × 660

were most concentrated around the Virchow-Robin spaces and infiltrated the surrounding brain. In many areas, the tumor cells surrounding neighboring vessels coalesced to form microscopic tumor nodules (Fig. 7).

The large left cerebral tumor and the smaller frontal lobe tumor probably arose from the confluence of these microscopic nodules. These large tumors were composed of abnormal reticulum cells with a small admixture of lymphocytes and plasma cells. The abnormal cells within the large tumors were also concentrated along the Virchow-Robin spaces and infiltrated the surrounding brain, Virchow-Robin spaces, and blood vessel walls (Fig. 8). The endothelial lining of the vessels was intact.

In a few areas, individual tumor cells, or small groups of cells, were enveloped by reticulin fibers, but, in general, there was no definite reticulum pattern. Many of the reticulum cells were argyrophilic when stained by the Weil-Davenport technic.

At the periphery of the tumors, there was a moderate reactive gliosis and the tumor cells infiltrated the brain singly and in small aggregates. The meninges overlying the basilar portion of the temporal lobe were focally involved by tumor cells.

In the anterior horn of the lumbar spinal cord, there was a small unilateral focus of gliosis and a perivascular infiltrate of lymphocytes, plasma cells, and lymphoid plasma cells. Intranuclear PAS-positive material was present in 2 or 3 of the lymphoid plasma cells. Abnormal reticulum cells were also present in this area.

**Spleen.** The lymphoid follicles were large, and a few had germinal centers. The cells of the follicles appeared to be normal. The cords of Billroth contained lymphocytes, plasma cells, and lymphoid plasma cells. Abnormal reticulum cells, morphologically identical to those in the brain tumors, were scattered singly or in small aggregates throughout the cords of Billroth (Fig. 9).

**Lymph nodes.** The sinuses of the abdominal lymph nodes contained an infiltrate similar to that in the splenic cords.

**Bone marrow.** Numerous apparently normal lymphoid follicles were noted, each with a germinal center. Scattered throughout the marrow spaces between these lymphoid folli-

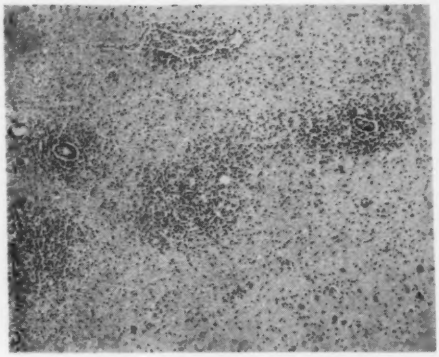

Fig. 7. Left cerebrum. A small cell infiltrate within Virchow-Robin space and a surrounding infiltrate of abnormal reticulum cells are seen. Note coalescence of tumor cells from neighboring vessels. Hematoxylin and eosin stain. × 90

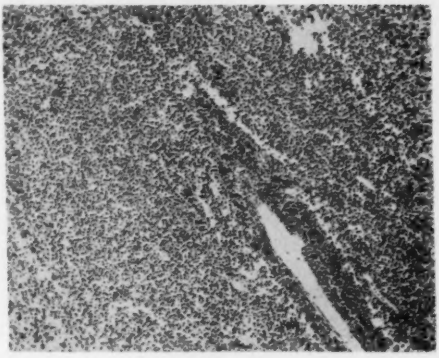

Fig. 8. Left cerebral tumor. A concentration of abnormal reticulum cells within and around Virchow-Robin space is seen. The brain has been completely replaced by the tumor cells. Hematoxylin and eosin stain. × 660

cles were the normal marrow constituents and small aggregates of lymphocytes, plasma cells, and lymphoid plasma cells. Cells with the intranuclear PAS-positive material were numerous. No abnormal reticulum cells were seen.

**Liver.** The portal areas were infiltrated by lymphocytes and an occasional abnormal reticulum cell. Lymphoid plasma cells with or without the intranuclear material were rare.

**Kidney.** In the perivascular regions within the renal parenchyma and throughout the fat of the renal pelvis, there were infiltrates of varied cellularity like those in the splenic cords. The small lymphocytes here appeared abnormal and had marked irregularities of the nuclear outline. Lymphoid plasma cells with the PAS-positive intranuclear material were frequently seen, and there were many mast cells associated with the infiltrates.

## DISCUSSION

Since the Bing-Neel syndrome consists of macroglobulinemia with central nervous system manifestations, the initial portion of this discussion will be concerned with the salient features of the macroglobulinemia first described in 1944 by Waldenström.[9]

Normally, approximately 4% of the total serum protein is a macroglobulin with an ultracentrifugal sedimentation rate of 18S, a molecular weight of approximately 1,000,000, and a hexose content 4 to 5 times that of normal gamma globulins. The serum protein in Waldenström's macroglobulinemia contains 5% or more macroglobulin.[6]

Clinically, this disease is characterized by fatigue, epistaxis, gingival hemorrhage, moderate lymphadenopathy, and hepatosplenomegaly. Elderly men are most commonly affected. The duration of the disease from onset to death is extremely variable.

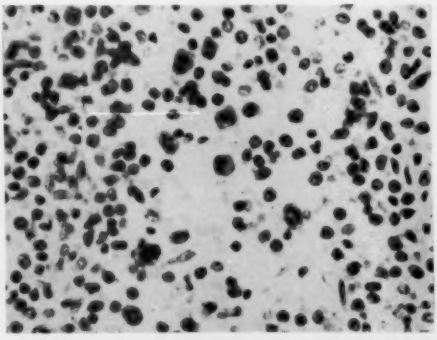

Fig. 9. Spleen. Small aggregate of abnormal reticulum cells in cord of Billroth. Compare with cells shown in Figure 6. Hematoxylin and eosin. × 660

Characteristic laboratory abnormalities are normocytic anemia, hyperglobulinemia with increased serum macroglobulins, markedly elevated erythrocyte sedimentation rate, bone marrow lymphocytosis, positive Sia test for euglobulins, cryoglobulins (15% of cases), abnormal liver function, and, rarely, Bence Jones proteinuria.[1,8]

Histologically, multiple organs—most commonly the lymph nodes, bone marrow, liver, and spleen—are involved by an infiltrate of variable cell types. Usually, the predominant cells are mature lymphocytes or plasma cells, but the infiltrates are occasionally composed of immature lymphocytes, plasma cells, or reticulum cells. The occurrence of a cell type which has a lymphocytic nucleus situated eccentrically in a plasmocytic cytoplasm has been frequently noted. The presence of PAS-positive intranuclear material in these lymphoid plasma cells has been reported.[1,10]

Because of the cytologic variability of the infiltrate, the macroglobulinemia of Waldenström has been variously diagnosed as lymphocytic leukemia, multiple myeloma, reticulum cell sarcoma, reticulum cell hyperplasia, Hodgkin's disease, and "unknown toxi-infectious disorder."[1,5,8] Since Waldenström's contribution, ultracentrifugation of the serum has established the diagnosis of macroglobulinemia. It is currently believed by most observers that Waldenström's macroglobulinemia is a neoplasia of the reticuloendothelial system, but its relationship to the malignant lymphomas and multiple myeloma is not clear.

The Bing-Neel syndrome, originally placed in a "toxi-infectious" category, appears to be the result of involvement of the central nervous system by this diffuse neoplasm. Involvement of the central nervous system in macroglobulinemia is probably infrequent since only a few instances of Bing-Neel syndrome have been recorded, while over 100 cases of Waldenström's macroglobulinemia without central nervous system involvement have been reported.[8]

The neurologic signs and symptoms described in the reported cases of Bing-Neel syndrome are extremely variable, and there is no characteristic clinical pattern. Diminished visual acuity or "cloudy vision" is a frequent complaint, and the ocular abnormalities which cause this have been described by other authors.[8,11] The vague psychic complaints, neuralgias, hearing loss, variable sensory disturbances, paresthesias, and paresis without increased intracranial pressure suggest a diffuse process such as radiculomyelomeningoencephalitis, cerebral arteriosclerosis, or degenerative disease.[2,3,5] In the present case, the occurrence of a demonstrable intracranial tumor and increased intracranial pressure complicated the differential diagnosis with the additional consideration of various brain tumors.

The combination of neurologic abnormalities and the clinical features described by Waldenström are consistent with a malignant lymphoma with central nervous system involvement or multiple myeloma. Lymphomas, especially chronic lymphocytic leukemia, may be impossible to differentiate clinically from macroglobulinemia. Multiple myeloma, with characteristic osteolytic lesions, can often be excluded since bone lesions have been rarely encountered with macroglobulinemia.[8] Routine bone marrow or lymph node examinations may or may not differentiate these diseases. The conclusive proof lies in the demonstration of increased serum macroglobulins by ultracentrifugal analysis and, perhaps, the presence of intranuclear PAS-positive material in lymphoid plasma cells.

In the previously reported cases of Bing-Neel syndrome, the histopathologic alterations within the brain and spinal cord consisted of dense cellular infiltrates confined to the Virchow-Robin spaces. The mature lymphocytes in the infiltrate suggested a possible meningoencephalitis to some observers.[2,3,5] Involvement of extracerebral organs by a similar cellular infiltrate was also noted.

The present case differs from those previously reported in that there were gross brain tumors and microscopic intracerebral infiltrates in addition to the diffuse infiltration of the Virchow-Robin spaces. The brain tumors and infiltrates were composed of abnormal reticulum cells with a small admixture of lymphocytes and plasma cells. Similar abnormal reticulum cells were present in small aggregates in the spleen, liver, and kidneys. The cellular infiltrates in the Virchow-Robin spaces consisted of lymphocytes, lymphoid

plasma cells, plasma cells, and a few abnormal reticulum cells. This type of infiltrate was also found in the spleen, lymph nodes, bone marrow, kidneys, and liver.

The gross and microscopic features of the brain tumor in the subject we are reporting are similar to those observed in brain tumors variously described as reticulum cell sarcoma of the brain[12,13] or microgliomatosis.[14] As pointed out recently by Fisher, Davis, and Lemmen,[15] these 2 entities probably differ from each other only in a semantic sense. Ultracentrifugation of the serum has not been done in any of the previously reported cases of reticulum cell sarcoma of the brain with extracerebral organ involvement. Recently, Earle[16] studied the histochemical properties of a series of brain tumors. He used the PAS technic but did not include reticulum cell sarcoma of the brain.

Of the 8 patients with microgliomatosis reported by Russell, Marshall, and Smith,[14] 3 had diffuse infiltration of extracerebral organs by cells similar to those in the perivascular brain lesions. Through the courtesy of Professor Russell, we have had the opportunity to examine tissues from these 3 patients and they resemble those in the present case, except for some differences in the apparent maturity of the infiltrative cells. In each of the 3 cases, cells with intranuclear PAS-positive material were found in the brain lesions and/or in the extracerebral infiltrates and the intravascular plasma was strongly PAS-positive. This suggests that reticulum cell sarcoma of the brain (microgliomatosis) with cellular infiltration of extracerebral organs and macroglobulinemia with central nervous system involvement may be identical.

SUMMARY

The histopathologic and clinical features of a case of Bing-Neel syndrome—macroglobulinemia with central nervous system symptoms—are described. The unique feature of this case was an intracerebral reticulum cell sarcoma associated with a densely cellular infiltration of the Virchow-Robin spaces of the brain and similar cellular infiltrates in the spleen, lymph nodes, kidneys, liver, and bone marrow. These cellular infiltrates were composed of lymphocytes, plasma cells, lymphoid plasma cells, and a few abnormal reticulum cells. Many of the lymphoid plasma cells contained intranuclear PAS-positive material. It is suggested that microgliomatosis and reticulum cell sarcoma of the brain with peripheral organ involvement may be identical to macroglobulinemia with central nervous system involvement. The clinical findings in macroglobulinemia are briefly reviewed. The differential diagnosis between the Bing-Neel syndrome and other diffuse central nervous system diseases is discussed.

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# Adrenocortical function in epilepsy

## II. The role of corticosterone in the mechanism and management of epilepsy

Patrick F. Bray, M.D., Vincent C. Kelley, M.D., Ph.D., Gerardo Zapata, M.D., and Robert S. Ely, M.D.

THE BACKGROUND DATA which led to the comprehensive investigation of pituitary-adrenal function in epilepsy have been outlined previously.[1] A series of clinical observations has clearly pointed to the adrenal cortex-central nervous system as an active neurohumoral mechanism. Convulsions including status epilepticus,[2-4] electroencephalographic changes,[5-7] altered mental states,[8,9] and intracranial hypertension[10] have appeared as complications in patients receiving cortisone and ACTH. In Addison's disease, mental changes[11,12] and electroencephalographic abnormalities[13-15] have been seen; these abnormalities have improved with hormone replacement therapy.[11,15]

A comprehensive study was undertaken to determine whether pituitary-adrenal function was a significant clinical factor in the mechanism or management of convulsive disorders. In the first phase of the study,[1] a report of hydrocortisone "metabolism" was made. In view of the negative nature of these latter studies, it seems unlikely that hydrocortisone plays an important role in the mechanism or management of seizures.

This, the second phase of the study, was designed to evaluate the role of corticosterone (Compound B) in epilepsy. Corticosterone has attracted the attention of endocrinologists and steroid chemists because it is the second most abundant measurable steroid that is produced by the human adrenal cortex. Unlike the clinically useful hydrocortisone, no clear-cut biologic role has yet been ascribed to corticosterone. Whereas hydrocortisone has potent "glucocorticoid activity" (affecting organic metabolism) and DCA and aldosterone have strong "mineralocorticoid activity," corticosterone falls between both groups in terms of its biologic activity, that is, it has only moderate "mineralocorticoid" effect and weak "glucocorticoid" action. Electroshock threshold studies in rats has also provided data to warrant its further study. Corticosterone has no significant effect on electroshock threshold when given alone to rats.[16] However, when given in combination with DCA or hydrocortisone, it antagonizes the action of either substance, showing a tendency to "normalize" brain excitability.[17]

This study of corticosterone in the mechanism and management of epilepsy has included the following 3 phases:

- Laboratory studies of corticosterone in patients with epilepsy: [1] Plasma levels of corticosterone; [2] half life of corticosterone (half life is determined as the rate at which intravenously administered corticosterone disappears from the circulation.)
- The effect of oral corticosterone on the incidence of seizures in 5 patients with refractory epilepsy.
- The effect of intravenous Dilantin on corticosterone levels in dogs. Indications for the last phase arose because the authors and other workers have attempted earlier to explain measured alterations in adrenocortical

From the Department of Pediatrics, University of Utah College of Medicine, Salt Lake City, and the Utah State Training School, American Fork.

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Dr. Kelley's present address is the Department of Pediatrics, University of Washington School of Medicine, Seattle. Dr. Zapata is now with the School of Public Health, Harvard University, Boston.

function not from the seizure mechanism itself but from the action of the commonly used anticonvulsant, Dilantin.

## MATERIALS AND METHODS

The patients whose corticosterone "metabolism" was studied were divided into [1] Dilantin-treated epileptic patients (29); [2] phenobarbital-treated epileptic patients (6); and [3] untreated epileptic patients (12). All of these patients were residents of the Utah State Training School, and all were mentally retarded; 10 of the 47 had spastic cerebral palsy, and the incidence of spasticity was similar in each group. All of the patients had grand mal seizures, and some had associated focal motor or psychomotor episodes; none had petit mal epilepsy. The patients were not classified neurologically in any greater detail. Patients ranged in age from 4 to 49 years, but the majority were in the second, third, and fourth decades of life. The 3 study groups of epileptic patients included 32 females and 15 males, with a similar ratio in each of the groups.

The effect of corticosterone* on the incidence of seizures was noted in 5 patients with severe epilepsy who were incompletely controlled on full doses of standard anticonvulsants. Corticosterone was simply added to the established anticonvulsant regimen. The average monthly incidence of seizures was computed after a twelve-month observation period. For the first month of corticosterone treatment, a daily dose of 100 mg. was given, and, for the second month, a daily dose of 300 mg. was given. The patients were observed for drug side effects, with particular attention being paid to the signs of fluid retention. Electroencephalograms were made before institution of therapy, and comparison records were obtained while patients were receiving 300 mg. of corticosterone daily. Observations of mood and alertness were also made.

Intravenous Dilantin† was administered to 3 dogs in the dose of 3½ mg. per kilogram to study the drug's effect on plasma levels of corticosterone. The animals used were trained, unanesthetized, adult mongrel dogs, each weighing approximately 20 kg. A control blood sample was obtained, the Dilantin Sodium was then injected over a period of two minutes, and repeated blood samples were then taken at intervals of fifteen, thirty, sixty, ninety, and one hundred and twenty minutes.

All plasma samples for corticosterone determination were separated by centrifugation and stored in a freezer until used for analysis. Plasma concentrations of corticosterone were determined by the method of Sweat[18] as modified by Ely, Hughes, and Kelley.[19] Corticosterone half-life determinations were done by the infusion of corticosterone (free alcohol), commercially prepared as a 0.5% solution in 50% ethanol. This solution was mixed with 15 cc. of 5% dextrose solution and given intravenously over a thirty-minute period. The dose of corticosterone was 2 mg. per killogram of body weight. Blood specimens for the determination of corticosterone were collected at thirty, sixty, ninety, one hundred and twenty, and one hundred and eighty minutes. The plasma concentrations of corticosterone at each interval were plotted against time, and the half life was calculated from the slope of the regression line.

## RESULTS

The laboratory studies of corticosterone "metabolism" in patients with epilepsy are presented in Table 1, which shows the mean plasma levels of corticosterone in each of the study groups. Significant elevation can be noted in each group. In contrast to a mean normal corticosterone value of 4 μg. per cent, the untreated patients have a level of 10.2 μg. per cent; the Dilantin-treated patients, 13.8 μg. per cent; and the phenobarbital-treated patients, 13.2 μg. per cent. Table 1 also indicates that, in contrast to the normal corticosterone half life of thirty-nine minutes, one finds prolonged values in both the untreated patients (fifty-seven minutes) and in the Dilantin-treated patients (sixty-nine minutes). The half life noted in phenobarbital-treated patients (fifty-one minutes) does not differ significantly from the normal. On inspection, the half life in this last group seemed prolonged initially, but the large standard

*Corticosterone was specially prepared for clinical use and was supplied through the courtesy of Joseph P. Webb, M.D., Upjohn Company.

†Dilantin Sodium Steri-Vials were supplied through the courtesy of Robert Hodgkinson, M.D., Parke-Davis and Co., Detroit.

TABLE 1

PLASMA LEVELS AND HALF LIFES OF CORTICOSTERONE

| Group | Plasma corticosterone concentrations (μg.%) Number of determinations | Mean | Standard error of mean | (p vs. normal) | Half life (minutes) Number of determinations | Mean | Standard error of mean | (p vs. normal) |
|---|---|---|---|---|---|---|---|---|
| Normal | 35 | 4.0 | 0.38 | – | 21 | 39 | 1.7 | – |
| Untreated epileptic | 15 | 10.2 | 1.5 | <0.01 | 11 | 57 | 3.7 | <0.01 |
| Dilantin-treated epileptic | 28 | 13.8 | 2.8 | <0.01 | 27 | 69 | 3.8 | <0.01 |
| Phenobarbital-treated epileptic | 6 | 13.2 | 2.2 | <0.01 | 6 | 51 | 11.3 | >0.1 |

error of the mean, 11.3 minutes, undoubtedly has influenced its statistical significance. The groups of Dilantin-treated patients have been subdivided into [1] well controlled and [2] poorly controlled. In Table 2, the plasma corticosterone levels and half lives for these subdivisions are compared. No significant difference is seen between the 2 groups.

The effect of corticosterone on the incidence of grand mal seizures in a group of 5 patients with refractory epilepsy is shown in Table 3. The corticosterone was simply added to the patients' current anticonvulsant regimen. It is apparent that the hormone had no significant beneficial effect on the seizure incidence. No clinical evidence of significant fluid retention was noted after body weight was carefully observed in all of the patients. Surprisingly, 4 of the 5 patients became more alert, happier, and less lethargic after discontinuation of the corticosterone. This change in the state of alertness and/or mood probably reflected a mild sedative or depressant effect of the medication. All 5 patients had electroencephalograms before and during maximum dose corticosterone therapy. None of the recordings showed significant improvement in response to therapy. The amount of seizure activity appeared to be increased in 3 patients, was unchanged in 1, and was lessened in 1.

The authors and other workers had suggested in earlier publications that measured alterations in adrenocortical function might have resulted not from the seizure process itself but from the commonly used anticonvulsant, Dilantin. For this reason, Dilantin was given intravenously to 3 dogs to study the drug's effect on plasma levels of corticosterone. Table 4 indicates that Dilantin had no consistent effect on the concentration of this hormone in dogs.

## DISCUSSION

The role of corticosterone in normal biologic function has remained uncertain. For this reason, it is difficult to assess abnormal "metabolism" of this hormone in a disease state like epilepsy unless it could be established as a useful therapeutic tool. This study revealed that epileptic patients as a group have high blood levels of corticosterone. Also, when large amounts of this hormone are given

TABLE 2

COMPARISON OF WELL CONTROLLED AND POORLY CONTROLLED DILANTIN-TREATED PATIENTS

| Group | Plasma corticosterone concentrations (μg.%) Number | Mean | Standard error of mean | p | Half life (minutes) Number | Mean | Standard error of mean | p |
|---|---|---|---|---|---|---|---|---|
| Well controlled | 21 | 14.3 | 3.6 | – | 20 | 67 | 3.7 | – |
| Poorly controlled | 7 | 13.1 | 3.2 | >0.1 | 7 | 75 | 10.2 | >0.1 |

intravenously to these same patients, the material is removed more slowly from the blood than in normal individuals. These abnormalities cannot be attributed to Dilantin therapy because the same findings were noted in patients who were receiving no treatment. Also, it was shown in one phase of this study that Dilantin has no significant influence on the blood levels of corticosterone in dogs when given in a single dose.

One might speculate that the high blood levels and slow disappearance rates of corticosterone reflected the body's attempt at "adaptation," that is, to "normalize" an abnormally low seizure threshold in the epileptic patient. Woodbury's[17] experimental demonstration that corticosterone has such an effect on the rat would lend support to such an hypothesis. If such a theory were correct, a beneficial therapeutic effect from corticosterone might be expected when the agent was given in large doses. However, it has been pointed out that corticosterone had no such anticonvulsant action when given to a small number of epileptic patients refractory to other standard anticonvulsants. The fact that no difference was noted between the well-controlled and poorly controlled patients also militates against the "adaptation" theory.

It seems very unlikely that these findings might represent a specific metabolic defect inasmuch as the patients who were studied undoubtedly were suffering from different basic neurologic defects. It is possible also that a slow rate of urinary excretion could account for the high and persistent blood levels in these patients, but, since no urinary corticosterone concentrations could be measured, this hypothesis could not be tested.

TABLE 3

EFFECT OF CORTICOSTERONE THERAPY ON INCIDENCE OF SEIZURES

| | *Number of seizures per month* | | | |
|---|---|---|---|---|
| | | *Corticosterone treatment* | | |
| *Case* | *Pre-corticosterone* | *100 mg. per 24 hours* | *300 mg. per 24 hours* | *Post-corticosterone* |
| L.N. | 3 | 8 | 7 | 10 |
| E.L. | 2 | 2 | 3 | 4 |
| D.M. | 6 | 4 | 2 | 1 |
| T.P. | 4 | 8 | 19 | 11 |
| K.W. | 3 | 7 | 3 | 5 |

TABLE 4

EFFECT OF INTRAVENOUS DILANTIN ON PLASMA CORTICOSTERONE LEVELS IN DOGS

| | *Plasma corticosterone levels (μg.%)* | | | | | |
|---|---|---|---|---|---|---|
| | *Control* | *15 minutes* | *30 minutes* | *60 minutes* | *90 minutes* | *120 minutes* |
| Dog 1 | 2.7 | 2.9 | 1.9 | 2.3 | 3.7 | 9.8 |
| Dog 2 | 2.6 | 2.3 | 3.1 | 2.4 | 2.3 | 2.0 |
| Dog 3 | 2.7 | 4.4 | 4.5 | 6.4 | 3.0 | 5.8 |

## SUMMARY

A study of the role of corticosterone in the mechanism and management of epilepsy has been carried out. The metabolism of hydrocortisone, an adrenal hormone with known biologic usefulness, was reported previously and was not significantly different from the normal. This search for adrenal cortex-central nervous system interaction was prompted by a series of clinical and laboratory observations, which are outlined in the introduction.

Both treated and untreated epileptic patients were found to have elevated blood levels of corticosterone. Half-life determinations of corticosterone were prolonged in both the untreated and Dilantin-treated patients. Intravenous Dilantin failed to produce significant changes in dogs' corticosterone levels.

The only tenable explanation for the persistently elevated levels of corticosterone seemed to be that the elevated levels reflected the body's attempt to "normalize" an abnormally low seizure threshold. Such a theory would be supported by experimental animal evidence. However, no beneficial therapeutic effect was noted when corticosterone was given to 5 patients with refractory major seizures, and findings did not differ between the well-controlled and poorly controlled patients.

The authors wish to express appreciation to Doris F. Tippit and Jennie Davis for their technical assistance.

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# Effect of intrathecal hydrocortisone on advanced adhesive arachnoiditis and cerebrospinal fluid pleocytosis

## An experimental study

Shaul Feldman, M.D., and Albert J. Behar, M.D.

FIBROUS ADHESIONS of any etiology in the subarachnoid space are always of serious clinical significance. The study of their pathogenesis and possible treatment in experimental animals is therefore of both practical and theoretic interest.

In a previous paper, we demonstrated that the intracisternal injection of talcum in cats caused the progressive development of fibrous pia-arachnoid adhesions. This process, as judged by the progressively increasing intricacy of the reticulin network and the thickening of the reticulin fibrils supporting the adhesions, was seen to begin at the end of the first week and to be well advanced by the end of the third week. The adhesive process was still in progress during the seventh week.[1] When cortisone or hydrocortisone were administered intracisternally after the end of the first week, the formation of the pia-arachnoid adhesions was either delayed or prevented.[2]

The primary purpose of the present investigation was to determine whether the intracisternal administration of hydrocortisone arrests the progressive growth of the reticulin network of pia-arachnoid fibrous adhesions after formation has begun.

We also examined the variations in the number of inflammatory cells in the cerebrospinal fluid during the course of repeated intracisternal injections of hydrocortisone in the experimental animals. This study was undertaken because the meningeal reaction to intrathecally administered hydrocortisone, as indicated by pleocytosis of the cerebrospinal fluid, is of practical importance because the hormone is administered by this route to patients with inflammatory and degenerative diseases of the central nervous system.[3–8]

### METHODS AND MATERIALS

In these experiments, 34 cats weighing 2.2 to 3.5 kg. were used. Cisternal punctures under sterile precautions were performed on the animals under light ether anesthesia. Finely ground talcum suspended in saline (100 mg. per cubic centimeter) was introduced into the cisterna magna of the animals after the withdrawal of a corresponding quantity of cerebrospinal fluid; 0.2 cc. of this sterile talcum suspension was administered per kilogram of body weight. Hydrocortisone acetate was injected intracisternally in 14 of these cats under sterile precautions every two or three days, in doses of 2 to 3 mg. per kilogram of body weight. The hydrocortisone treatment was started at the following intervals after introduction of the talcum: in 4 animals on the nineteenth day, in 1 on the sixteenth day, in 3 on the fourteenth day, in 1 on the thirteenth day, in 1 on the twelfth day, in 2 on the eleventh day, and in 2 on the tenth and ninth day, respectively (see table).

For control purposes, 20 animals that had

From the Department of Nervous Diseases, the Laboratory of Experimental Neurology, and the Department of Pathology, Rothschild Hadassah University Hospital and the Hebrew University–Hadassah Medical School, Jerusalem, Israel.

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SCHEDULE OF EXPERIMENTAL TREATMENT

| Cat | Beginning of treatment after intracisternal talcum injection (days) | Number of intracisternal injections of hydrocortisone | Total days of experiment |
|---|---|---|---|
| T 225 | 9 | 8 | 31 |
| T 226 | 10 | 5 | 26 |
| T 220 | 11 | 3 | 18 |
| T 215 | 11 | 3 | 18 |
| T 217 | 12 | 6 | 25 |
| T 222 | 13 | 3 | 20 |
| T 211 | 14 | 8 | 34 |
| T 218 | 14 | 7 | 32 |
| T 212 | 14 | 5 | 28 |
| T 219 | 16 | 7 | 32 |
| T 203 | 19 | 2 | 24 |
| T 205 | 19 | 6 | 34 |
| T 204 | 19 | 7 | 35 |
| T 202 | 19 | 8 | 41 |

not received hydrocortisone treatment were killed at different times seven to forty-three days after talcum injection.

The animals treated with hydrocortisone died or were sacrificed with ether anesthesia between the first and third week after the first injection. The brains were removed and fixed in 4% neutral formalin for two weeks.

Paraffin-embedded slices of the brains were prepared for histologic examination; these included several standard sections along the brain stem. The histologic studies of the brains of control and hydrocortisone-treated animals at comparative chronologic stages were mainly confined to such standard sections. Only those animals in which the subarachnoid space was filled with talcum particles were considered in this study. Histologic sections were stained with hematoxylin and eosin and Laidlaw's procedure for reticulin fibrils. The degree of development of pia-arachnoid adhesions was determined by the degree of intricacy of their supporting reticulin network as well as by the increase in thickness of the individual reticulin fibrils.[1]

White cells were counted in the cerebrospinal fluid samples withdrawn before most injections of hydrocortisone.

Bacteriologic cultures of 10 samples of spinal fluid withdrawn from various animals in the course of their treatment with intracisternal injections of hydrocortisone were made in order to rule out a secondary infection of the meninges subsequent to the repeated injections.

HISTOLOGIC EXAMINATIONS

**Control animals.** During the *second week* after talcum injection, local histiocytic (arachnothelial) cells transformed into mobile macrophages were quite abundant and were found

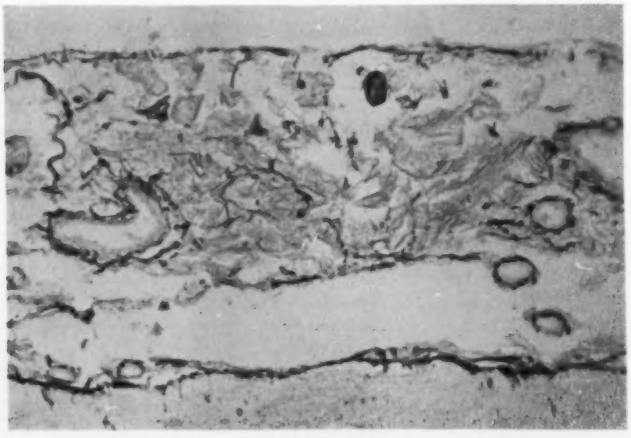

Fig. 1. Subarachnoid space of control animal in second week after intracisternal injection of a suspension of talcum particles. Among talcum particles, short and thin reticulin fibrils are seen not fused together into a network. Laidlaw's reticulin stain. × 140

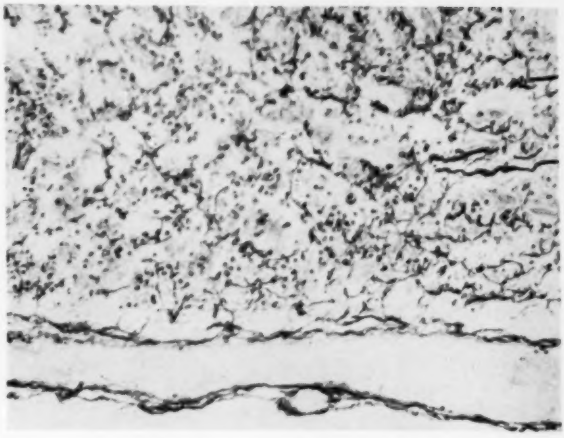

Fig. 2. Subarachnoid space of control animal in third week after intracisternal talcum injection. Reticulin fibrils are long and at many points join each other to enmesh groups of talcum particles and to form a widespaced network. Laidlaw's reticulin stain. × 140

attached to many talcum particles within the subarachnoid space. Simultaneously, fine reticulin fibrils had appeared, forming a widely spaced network enmeshing large groups of talcum particles (Fig. 1).

During the *third week* after talcum injection, the macrophages formed a quite dense granulomatous tissue enclosing talcum particles and obliterating the subarachnoid space. The reticulin network within these areas was more intricate than the one noted in the second week, and its fibrils were thicker (Fig. 2).

During the *fourth and fifth weeks,* there was an increasing tendency of the macrophages to surround talcum particles and to coalesce into larger syncytial masses which engulfed the particles. The reticulin network tended to increase in intricacy and thickness of fibrils and intersected the talcum masses into progressively smaller groups (Fig. 3).

**Hydrocortisone-treated animals.** *Group I* was comprised of 9 animals in which treatment was started during the second week after intracisternal talcum administration and which were sacrificed in the third, fourth, and fifth weeks of the experiment (see table). In 7 of

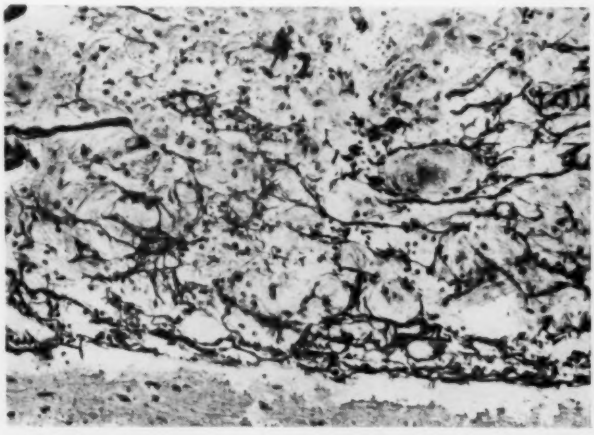

Fig. 3. Subarachnoid space of control animal in fifth week after intracisternal talcum injection. Reticulin fibrils are long and thicker than those seen earlier and join to form quite an intricate network encircling individual talcum particles. Laidlaw's reticulin stain. × 140

these, an arrest in the proliferative activity of the local leptomeningeal macrophages as well as in the development of the reticulin network within the subarachnoid space was observed. This arrest occurred apparently at the time the hydrocortisone administration was started. Thus, in spite of the fact that these animals had lived for three to five weeks after the talcum injection, the histologic picture in all of them was similar to that observed in control animals two weeks after talcum injection (Fig. 4). However, in 1 (T 225) of the remaining 2 animals, sacrificed in the fifth week after talcum injection, the histologic picture in the leptomeninges and subarachnoid space of the brain was identical with that observed in control animals sacrificed at the same time. On the other hand, in the second remaining animal (T 217) sacrificed four weeks after talcum injection, the histologic picture in the leptomeninges and pia-arachnoid space showed a less advanced arachnoiditis than found in control animals in the second week after talcum administration.

*Group II* was comprised of 5 animals in which treatment was started during the third week after intracisternal talcum administration and which were sacrificed in the fourth, fifth, and sixth weeks of the experiment (see table). In 2 of these (T 204 and T 219), sacrificed in the fifth week after talcum injection, an arrest in the development of pia-arachnoid adhesions, including the reticulin network, was observed. The histologic picture (Fig. 5) was identical with that in control animals sacrificed in the third week. In 1 treated animal (T 203) sacrificed in the fourth week after talcum injection, the histologic picture was similar to that in controls sacrificed at the same time. In another 2 animals (T 205 and T 202) killed in the fifth and sixth weeks, respectively, the histologic picture in the leptomeninges and subarachnoid space corresponded to those found in control animals two weeks after talcum injection. The findings in these latter 2 animals suggest that the adhesive process had regressed from the point it had reached before the start of hydrocortisone treatment.

### CEREBROSPINAL FLUID EXAMINATIONS

In Figure 6, the cerebrospinal fluid white cell counts on different days after the commencement of hydrocortisone injections are shown. As previously reported[1] and as found in the present experiments, the cerebrospinal fluid white cell counts were low in the second and third weeks after intracisternal administration of talcum, that is, just before the beginning of hydrocortisone administration. The first injection of hydrocortisone induced in most animals a cerebrospinal fluid white cell pleocytosis, which subsided in spite of repeated intracisternal injections of hydrocortisone. No bacteria were grown on cultures of the fluid.

Fig. 4. Subarachnoid space of animal treated with hydrocortisone from second week after intracisternal talcum injection and sacrificed three weeks later. Development of reticulin fibrils is similar to that in control animals in second week (Fig. 1). Laidlaw's reticulin stain. × 140

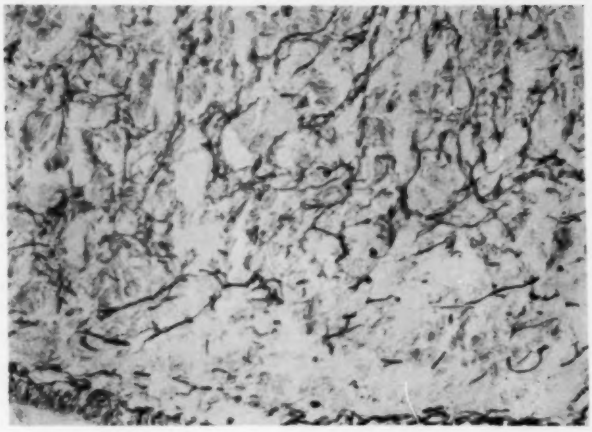

Fig. 5. Subarachnoid space of animal treated with hydrocortisone from third week after intracisternal injection of talcum and sacrificed three weeks later. Development of reticulin network is similar in degree to that in controls during third week (Fig. 2). Laidlaw's reticulin stain. × 140

COMMENT

From the comparison of our control and hydrocortisone-treated animals, it becomes apparent that the development of pia-arachnoid adhesions was arrested in most animals at the stage at which hydrocortisone administration was initiated. For example, Figure 4 demonstrates that, in an animal treated with hydrocortisone from the fourteenth day after an intracisternal talcum injection and killed three weeks later, the degree of development of the pia-arachnoid adhesions was equal to that in a control animal killed at the end of the second week after talcum injection (Fig. 1).

The clinical inference of these results may be that hydrocortisone should be administered as early as possible to patients with evidence of developing pia-arachnoid adhesions.

In 2 animals, hydrocortisone had no obvious effect on the developing pia-arachnoid adhesions. This may be explained by an individual unresponsiveness to the adrenocortical hormone. The finding in 3 cats of an apparent regression of the adhesions after hydrocortisone administration is of interest and certainly requires further investigations.

It had previously been reported that, while a single injection of cortisone into the cisterna magna of normal cats caused a transient pleocytosis in the cerebrospinal fluid, subsequent administrations of the hormone provoked only a very slight meningeal reaction.[9] This phenomenon was reexamined in this study, since hydrocortisone is less soluble than cortisone in body fluids and also to find out whether the response of inflamed and normal meninges to the introduction of the hormone is similar.

The meningeal response to intrathecal injection of hydrocortisone in patients has been recorded in several clinical reports. In most patients suffering from different neurologic conditions, the treatment was well tolerated

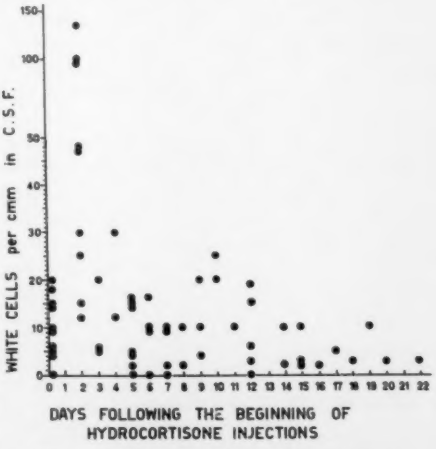
WHITE CELLS per cmm in C.S.F.
150
100
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
DAYS FOLLOWING THE BEGINNING OF HYDROCORTISONE INJECTIONS

Fig. 6. Variations in white cell count in cerebrospinal fluid after repeated intracisternal injections of hydrocortisone acetate

and no or very few white cells appeared in the cerebrospinal fluid.[4,5] On the other hand, clinical signs of meningeal irritation and cerebrospinal fluid pleocytosis have been observed in a few patients who received hydrocortisone intrathecally.[6–8] Furthermore, Dereux, Vandenhaute, and Deheck[10] reported the development of spinal subarachnoid block after repeated intrathecal injections of hydrocortisone in a patient with multiple sclerosis.

Almost every substance, including isotonic sodium chloride solution,[11,12] will cause pleocytosis when introduced into the subarachnoid space. Thus, repeated intrathecal injections of penicillin into the normal subarachnoid space will cause an increasing and prolonged cellular reaction.[13] With some substances, this meningeal reaction is very considerable and, if accompanied by other toxic manifestations, may be of grave clinical significance. This is one main reason for discarding intrathecal administration of streptokinase and streptodornase in the treatment of tuberculous meningitis.[12,14]

The present investigation shows that the introduction of hydrocortisone into the inflamed subarachnoid space causes an initial and moderate meningeal cellular reaction, whereas repeated injections produce only a very slight pleocytosis. A possible explanation of this is that the first injection of hydrocortisone induces a meningeal reaction, such as any other substance may, but that the response to subsequent injections into the subarachnoid space is inhibited by the antiinflammatory action of the previously administered hydrocortisone.

This investigation presents experimental evidence indicating that the adrenocortical hormones have an inhibitory effect on developing pia-arachnoid adhesions and demonstrates that repeated intrathecal injections of hydrocortisone in effective doses do not aggravate the inflammatory process in the subarachnoid space.

SUMMARY

The effect of intrathecal administration of hydrocortisone on the reticulin network of developing pia-arachnoid adhesion induced by talcum and on cerebrospinal fluid pleocytosis was determined. In most animals, hydrocortisone arrested further development of the reticulin network and of the cellular elements of the adhesions from the time of its administration. The first intrathecal administration of hydrocortisone caused a moderate pleocytosis in the cerebrospinal fluid, whereas subsequent injections produced only a very slight cellular reaction.

The results of the present investigation warrant early administration of adrenocortical therapy to patients with developing pia-arachnoid adhesions in order to inhibit further increase and suggest that such therapy, when given intrathecally, does not aggravate the inflammatory process in the subarachnoid space.

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# Dilantin in the treatment of lightning pains

Lt. Joseph B. Green, M.C., U.S.N.R.

THE TREATMENT of lightning pains due to tabes dorsalis by means other than narcotics has been largely ineffectual.[1] These radicular pains are frequently so severe as to completely incapacitate and occasionally lead to narcotic addiction. Iannone, Baker, and Morrell[2] reported that the similar lancinating pain of trigeminal neuralgia responded to Dilantin therapy. It was therefore decided to try this drug in two patients with tabes dorsalis, each of whom had lightning pains for many years. These cases will be reported in detail.

CASE REPORTS

**Case 1.** C. B., a 60-year-old man, had "shooting" pains since 1933. A syphilitic infection had been diagnosed four years before on the basis of pupillary changes and positive blood and cerebrospinal fluid serologic tests. Since that time, he had received 2 courses of bismuth and arsenic therapy and 2 courses of penicillin. The pains continued unabated, involving all extremities and the chest, especially the right costal margin. Attacks occurred up to twenty times daily and were characterized by a sudden onset which paralyzed locomotion or respiration for ten to fifteen seconds.

Radiation occurred distally down the affected extremity or anteriorly around the rib cage. No symptoms were referable to bladder or bowel function. He complained of difficulty in keeping his balance in the dark. At the time of the initial examination, he was unemployed, sustained work of any type being impossible because of the attacks of pain.

Neurologic examination revealed a mildly ataxic man with normal speech and mental status. The Romberg test was positive. Pupils were unequal, the left being dilated, and neither reacted to light. The reaction to accommodation was preserved on the right. The left optic disk was pale. The patellar reflexes were barely obtainable, and the Achilles jerks were absent. Deep pain sensibility was reduced in the Achilles tendons. Vibratory and position sense were moderately reduced in the toes and feet.

The blood Kolmer and Wasserman were weakly reactive. Examination of the cerebrospinal fluid disclosed a normal cell count (2 lymphocytes per cubic millimeter), a protein of 36 mg. per cent, and a negative serologic test. The colloidal gold curve was 2233455443.

Dilantin, 100 mg. three times a day, was instituted, and, by the third day of this therapy, there was a marked reduction in the frequency of the attacks. The next twelve months, while taking the drug regularly, the patient averaged only 3 attacks of shooting pain per week and reported that the pain when present was much less severe. He was able to resume his usual occupation as an aircraft worker. On discontinuing Dilantin, he found that the pains recurred in approximately forty-eight hours.

**Case 2.** H. Z., a 47-year-old woman, had lightning pains for twenty years, after appendectomy and ovariectomy. At that time, a routine blood serologic test was positive. It was determined that her husband also had a syphilitic infection. She received a course of bismuth and arsenic and, ten years later, a course of penicillin therapy. However, the pains continued and were unrelieved by a variety of medications. They occurred up to ten times daily and were present in the arms, legs, and chest. They were lancinating and radiated distally. She noted no difficulty with balance or bowel and bladder function.

Neurologic examination revealed irregular miotic pupils which failed to react to light but reacted promptly on accommodation. All deep tendon reflexes were unobtainable; position sense and deep pain sensibility were markedly reduced in the toes and feet. The Romberg test was positive. Mental status and speech were considered normal. She had recently received a lumbar puncture elsewhere, and the results were said to be negative or within normal limits. A blood serologic test was negative or nonreactive. Dilantin, 100 mg. three times a day, was started, and relief of the pains was noted in forty-eight hours.

On this therapy, she noted only 2 or 3 attacks per week and stated that when present the pain was not as severe as formerly. After six months, she discontinued the drug and the pains recurred in approximately forty-eight hours. These were

From the Neuropsychiatric Service, U.S. Naval Hospital, San Diego, Calif.

relieved within seventy-two hours after the Dilantin was restarted.

## DISCUSSION

The efficacy of Dilantin in controlling severe pain present more than twenty years in these two cases is not likely to be due to a placebo effect. As argued by Iannone and associates,[2] the delay in achieving results after institution of treatment as well as the time lag in return of symptoms after discontinuing the Dilantin correlate well with known pharmacologic properties of the drug. Morrell, Bradley, and Ptashne[3] demonstrated an inhibitory effect of Dilantin on threshold and conduction of mammalian peripheral nerve, suggesting a rationale for the use of the drug in clinical neuralgic states. Such states would appear to include the lightning pains of tabes dorsalis, as well as trigeminal and glossopharyngeal neuralgia.

## SUMMARY

Dilantin was administered to two patients with severe lightning pains due to tabes dorsalis. Remarkable relief was obtained in both cases.

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# Observations on ceruloplasmin and methods for its estimation

Sean O'Reilly, M.D.

THE TERMS serum oxidase, serum copper oxidase, and ceruloplasmin are frequently regarded as more or less synonymous in meaning, and an extensive literature on ceruloplasmin and serum oxidase has accumulated over the past twelve years. Ceruloplasmin is of considerable interest, not only for its biochemical features but because of its relationship to disease states, of which hepatolenticular degeneration (Wilson's disease) is the most important.

Although Mann and Keilin[1] in 1938 described the isolation from human blood of a copper-containing globulin and Luetscher[2] two years later found a similar blue globulin in pig's serum, it was not until 1947 that a series of papers by Holmberg and Laurell[3–6] led to a more adequate appreciation of the importance of the substance called by them ceruloplasmin because of its blue color.

It is said to be an alpha$_2$ globulin of a molecular weight of approximately 151,000 and to have a copper content of around 0.34%, which corresponds to 8 atoms of copper per molecule of ceruloplasmin. Holmberg and Laurell thought that most (90 to 95%) of the serum copper was bound to ceruloplasmin, and this is in agreement with the findings of others, such as Cartwright and associates.[7] However, Thompson and Watson,[8] using graded sodium sulfate precipitation of the globulins, and later Cumings, Goodwin, and Earl,[9] using the same technic and controlling by paper electrophoresis, showed association of a considerable proportion of the copper with fractions of different mobilities from alpha globulin.

The early studies by Holmberg and Laurell showed that ceruloplasmin, like such other copper proteins as plant laccase, has enzymatic activity as an oxidase against a variety of polyhydroxylic and polyamine compounds, which include pyrogallol, catechol, epinephrine, ascorbic acid, hydroquinone, and paraphenylenediamine (PPD). The last appears to be the best substrate, in vitro at least, and, while up to the present no very definite physiologic function can be assigned to ceruloplasmin, its enzymatic activity has led to a very useful method for its determination and its study by workers in many centers.

Scheinberg and Gitlin[10] showed that patients with hepatolenticular degeneration had little or no ceruloplasmin in their blood. Hepatolenticular degeneration is a rare, often familial, genetically determined disease. The first recorded case was observed by Frerichs of Berlin in 1854,[11] but it was not until 1912 that the clinical, historic, and pathophysiologic features were very ably described by Kinnier Wilson.[12] The condition has not ceased to intrigue and puzzle investigators ever since.

Current knowledge and theories on the subject are well reviewed by Bearn[13] and Walshe.[14] The 2 facts which are now generally accepted and which are relevant to this paper are as follows:

1. A number of clinical forms of the disease exists; in addition to the classic acute or subacute type with mainly neurologic features as described by Wilson and the chronic, long drawn out neurologic form equated in some of the European literature with pseudosclerosis of Westphal[15] and Strümpell,[16–18] primary abdominal forms have been described,[19–22] a

From the Department of Chemical Pathology, Institute of Neurology, Queen Square, London, and the Department of Neurology, University of California Medical Center, San Francisco.

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possibility first suggested by Bramwell[23] as long ago as 1916.

2. The vast majority of patients with Wilson's disease are found to have little or no ceruloplasmin in their blood, although, rarely, cases have been reported with normal or near-normal ceruloplasmin levels.[24]

Since, therefore, clinically atypical cases occur and since the biochemical abnormalities are presumably present for some time before clinical features develop,[25] the demonstration of such abnormalities is of considerable importance diagnostically. The defect in ceruloplasmin is perhaps the most constant abnormal feature and certainly the easiest to detect.

The chief purpose of this paper is to indicate the common methods used to measure ceruloplasmin and oxidase activity in the serum, to present the results of measuring the serum oxidase activity enzymatically by 2 different technics in 2 separate series of patients, to compare these results with those reported by other workers, and to indicate which of the 2 methods described is the most reliable.

The concentration of ceruloplasmin in the plasma or serum might be measured in a number of ways:

- By colorimetric determination of its blue color[4,25]
- By measurement of its ability to oxidize paraphenylenediamine[5,25–27]
- By immunochemical technics[10,28]
- By measurement of plasma or serum copper, since 90 to 95% is supposed to be bound to ceruloplasmin.[4]

Of the technics described, measurement of the enzymatic activity of ceruloplasmin using either paraphenylenediamine (PPD) or N–N, dimethyl paraphenylenediamine (DPPD) as substrate is perhaps the one most commonly used. The oxidase activity may be estimated in the Warburg apparatus by measuring the oxygen uptake, or it may be determined colorimetrically or spectrophotometrically by measuring the maximal absorbance of the colored oxidation products. In the case of PPD, this absorbance peak is in the wavelength range of 525 to 530 mμ.

Using a modification of the procedure de-

TABLE 1
FINDINGS ON OPTICAL DENSITIES AND SERUM COPPER LEVELS

| *Diagnosis* | *Number of cases* | *Range of optical density* | *Serum copper (μg. %)* |
|---|---|---|---|
| 1. Brain tumor (primary and metastatic) | 13 | 0.300 to 0.800 | 183 to 285 |
| 2. Diffuse degenerative brain disease | 19 | 0.200 to 0.800 | 106 to 230 |
| 3. Focal or localized degenerative brain disease | 36 | 0.260 to 0.900 | |
| 4. Epilepsy | 19 | 0.200 to 1.200 | 120 to 420 |
| 5. Mental defect | 10 | 0.375 to 0.700 | |
| 6. Schizophrenia and psychoneurosis | 36 | 0.150 to 0.600 | 68 to 340 |
| 7. Spinal cord—tumors | 5 | 0.155 to 0.430 | |
| 8. Spinal cord—inflammatory or degenerative disease | 17 | 0.235 to 0.800 | 128 to 277 |
| 9. Peripheral neuropathy | 13 | 0.275 to 0.750 | 153 to 306 |
| 10. Myopathies | 5 | 0.250 to 0.710 | |
| 11. Cirrhosis of the liver | 16 | 0.120 to 0.900 | |
| 12. Miscellaneous diseases | 12 | 0.150 to 0.720 | 120 to 350 |
| 13. Undiagnosed disease | 14 | 0.105 to 0.650 | 31 to 260 |
| 14. Newborn babies* | 9 | 0.102 to 0.230 | |
| 15. Normal persons | 9 | 0.250 to 0.650 | 90 to 250 |

*One of these had an optical density around 0.400–0.450.

scribed by Ravin,[27] blood from 9 normal persons, 9 newborn infants, and 215 patients has been examined at the University of California Medical Center in San Francisco. In some cases, repeated estimations were made, and, in most, serum copper measurements were also carried out by methods reported in the literature.[29,30] Of these methods, that described by Ressler and Zak[30] was found to give the most consistently reliable and reproducible results. Table 1 shows the breakdown of this group into diagnostic categories and the range of optical densities and serum copper levels.

Utilizing the technic described, Ravin found an optical density of the PPD oxidation product ranging from 0.1 to 0.3 in normal subjects. In the 9 such subjects examined by the author, the optical densities obtained were between 0.2 and 0.65. Of the patients and newborn infants examined, 166 fell within this range; 26 had an optical density above 0.65, 37 fell between 0.1 and 0.2, and 4 were below 0.1 (Fig. 1).

Of the 4 below 0.1, 2 had Wilson's disease, clinically beyond doubt and confirmed at autopsy, 1 had severe liver disease and died in hepatic failure, and 1 had a diagnosis of schizophrenia. These 2 were almost certainly incorrect results. Of the group between 0.1 and 0.2, 7 were newborn infants and 5 were patients with severe hepatic failure from a variety of causes, but there were 25 patients whose PPD oxidase activity appeared to be significantly lower than that of the normal subjects, for no obvious reason.

Because of these anomalies in the results and because in the course of the work difficulty was encountered in obtaining reproducible results as well as in maintaining the *p*H at 6.0, it was felt that Ravin's technic was not entirely satisfactory. From the biochemical point of view, the main criticism would appear to be that, at the *p*H suggested by Ravin, acetic acid–sodium acetate solutions have only a limited buffering capacity.

Accordingly, the following procedure, which is essentially the same as that described by Boyd-Houchin,[31] was used.

REAGENTS

1. Commercial PPD dihydrochloride was recrystallized according to a method suggested by Scheinberg (personal communication) and the pure white crystals stored in a vacuum jar over NaOH.

2. 0.075% PPD in acetate buffer of *p*H 5.2 was prepared before each series of tests.

3. Acetate buffer *p*H 5.2 ($\pm$ 0.05) was prepared fresh daily from 0.2M sodium acetate and 0.2M acetic acid.

4. Sodium azide, $3 \times 10^{-3}$M, to stop enzymatic reaction was prepared fresh daily from $10^{-1}$M sodium azide in 3% NaCl (stock solution stored in cold).

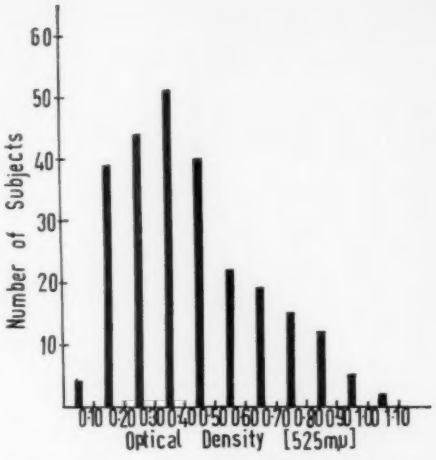


Fig. 1. PPD oxidase activity in 233 subjects (in terms of $E_{1cm}$ 525 mμ oxidation product)

TEST PROCEDURE

Place 1 cc. of PPD solution in a 15-cc. test tube and allow to stand in a water bath at 37° C. for fifteen minutes; then stop reaction by the addition of 3 cc. of ice-cold sodium azide solution. Measure optical density at 525 mμ against a reagent blank (1 cc. of substrate solution and 0.1 cc. of water) incubated at the same time or against zero time specimens consisting of 1 cc. of substrate, 3 cc. of sodium azide solution, and 0.1 cc. of serum, if a greater degree of accuracy is desired.

RESULTS

With this technic, the serum PPD oxidase levels of 135 patients were measured. The results are seen in Figure 2.

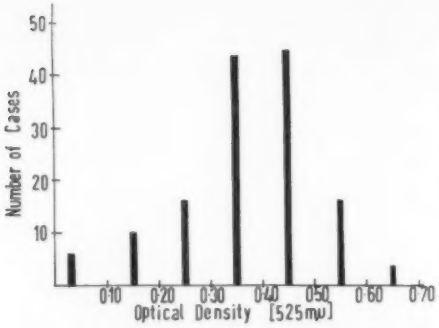


Fig. 2. PPD oxidase activity in 135 subjects (in terms of $E_{1cm}$ 525 mμ oxidation product)

It is apparent that the great majority (117 cases) fall within the range 0.2 to 0.6; there were 6 cases with little or no PPD oxidase activity, all clinically and biochemically certain cases of Wilson's disease. Only 10 readings were low normal, of which 5 were obtained in sera from nephrotic children, 2 from newborn babies, 1 from a patient with cirrhosis (suspected Wilson's disease but not yet proved), and 2 from the parents of a patient with known Wilson's disease.

No false results were obtained, and repeated examination of the same sera always gave a constant answer. The PPD oxidase activity of serum was found to be remarkably stable over many months if it was kept in the cold or frozen; however, bacterial contamination resulted in rapid and marked loss of activity. Similar loss was seen with frozen serum which was frequently tested; repeated freezing and thawing appeared to damage the enzymatic activity, an experience noted also with purified ceruloplasmin by Curzon and Vallet.[32]

TABLE 2
CORRELATION OF SERUM OXIDASE AND CERULOPLASMIN CONTENT

| *Patient* | *Ceruloplasmin (mg.%) cyanide decolorization* | *PPD oxidase (in terms of optical density)* | *Diagnosis* |
|---|---|---|---|
| J.S. | 33.5 | 0.295 | Huntington's chorea |
| B.C. | 33.8 | 0.310 | Schizophrenia |
| R.B. | 49 | 0.380 | Cirrhosis |
| R.B. | 30.4 | 0.312 | Late cerebellar ataxia |
| Von B. | 12.6 | 0.110 | Wilson's disease |

TABLE 3
CORRELATION OF OPTICAL DENSITY, OXYGEN UPTAKE, AND SERUM COPPER

| *Patient* | *Average optical density* | *Serum copper (μg.%)* | *$O_2$ uptake (Warburg) (microliters per cc. per hour)* |
|---|---|---|---|
| No. 1 | 0.524 | 156 | 287 |
| No. 2 | 0.394 | 143 | 222 |
| No. 3 | 0.355 | 123 | 182 |
| No. 4 | 0.284 | 103 | 158 |
| No. 5 | 0.208 | 110 | 199 |
| No. 6 | 0.378 | 103 | 170 |
| No. 7 | 0.278 | 167 | 239 |
| No. 8 | 0.239 | 128 | 244 |
| No. 9 | 0.136 | 83 | 128 |
| No. 10 | 0.195 | 100 | 157 |
| No. 11 | 0.251 | 125 | 163 |
| No. 12 | 0.275 | 130 | 202 |
| No. 13 | 0.501 | 150 | 262 |
| No. 14 | 0.155 | 103 | 153 |
| No. 15 | 0.164 | 103 | 145 |
| No. 16 | 0.390 | 120 | 134 |
| No. 17* | 0.130 | 110 | 103 |
| No. 18† | 0.053 | 66 | 25.5 |
| No. 19† | 0.033 | 43 | 0 |
| No. 20† | 0.006 | 33 | 0 |
| No. 21† | 0.010 | 46 | 0 |
| No. 22† | 0.019 | 50 | 0 |
| No. 23† | 0.014 | | |

*Wilson's disease suspected
†Definitely diagnosed Wilson's disease

Good correlation was noted between serum oxidase levels measured in this way and ceruloplasmin content measured spectrophotometrically after decolorization by sodium cyanide, as described by Scheinberg and associates[26] (Table 2).

Sera from 23 patients, of whom 6 had Wilson's disease, had their oxygen uptake in the presence of PPD measured on the Warburg apparatus. In general, there was a reasonable correlation between optical density 525 mμ, $O_2$ uptake, and the serum copper, as shown in Table 3. Ceruloplasmin standard solution (10 mg. per cent) had an optical density of 0.1, a copper content of 36 μg. percent, and an oxygen uptake of 129 $\mu LO_2$ per cubic centimeter per hour.

It was decided to check the effect of as-

corbic acid on PPD oxidation by ceruloplasmin standard solutions in view of findings which are discussed fully below.

The results summarized in Table 4 indicate that the addition of ascorbic acid in the concentrations in which it is normally found in the blood had no significant effect on PPD oxidation by ceruloplasmin under the conditions of the technic described earlier.

## DISCUSSION

The results presented above are largely in agreement with those of other workers. Thus, as reported originally by Scheinberg and Gitlin,[10] most of the patients with Wilson's disease had little or no ceruloplasmin or oxidase activity in their serum, whether measured by spectrophotometric technics after sodium cyanide decolorization or by enzymatic methods using PPD or DPPD as substrate.

However, 1 patient with Wilson's disease, Von B. in Table 2, in whom the diagnosis was confirmed at autopsy, had near-normal levels of PPD oxidase activity and of serum ceruloplasmin. Such cases are uncommon, as indicated by Sass-Kortsak,[24] but another of the patients examined, No. 17 in Table 3, in whom the diagnosis of Wilson's disease was suspected because of the findings of unexplained cirrhosis and Kayser-Fleischer rings, had low-normal ceruloplasmin, PPD oxidase activity, and serum copper. This patient has, up to the present, no neurologic findings and is very similar to the first of the cases discussed by Warnock and Neill.[22]

Scheinberg, Cook, and Murphy[33] reported that, while the plasma ceruloplasmin in pregnant women at term was high, the concentration in the blood of their newborn babies was uniformly low. The small number of newborn babies examined in the course of the investigations above reported had serum oxidase activity in the low-normal range, with one exception, a baby who had convulsions from the time of delivery. Her serum oxidase activity on the third postpartum day approximated to average normal adult levels.

The only other condition in which ceruloplasmin and serum oxidase levels may be below normal is the nephrotic syndrome, where ceruloplasmin is lost in the urine.[28] The 5 patients with nephrotic syndrome who had serum oxidase measurements made during the course of investigations here reported all had low-normal levels; 3 of them were losing 1 gm.+ of protein in their urine, and it was possible to demonstrate PPD oxidase activity in the urine of these 3 patients.

It is clear from the results obtained in both series that the majority of the patients examined had levels of serum PPD oxidase activity that fell within the range obtained in normal subjects. The spectrum of diseases represented by the patients was much the same in both series and covered a fairly broad range of neurologic and other conditions. It can be said, however, that, in general, patients with infections and organic disease of the nervous system tended to have significantly higher levels than the average normal person. Some of the highest figures obtained in the investigations were from patients with a severe convulsive disorder or diffuse or focal brain disease, especially neoplastic lesions.

TABLE 4
EFFECT OF ASCORBIC ACID ON PPD OXIDATION BY CERULOPLASMIN STANDARD SOLUTIONS

| *Ceruloplasmin solution (mg. %)* | *Without ascorbid acid* | *With ascorbic acid (1.2 mg. %)* | *With ascorbic acid (1 mg. %)* | *With ascorbic acid (0.7 mg. %)* |
|---|---|---|---|---|
| I 150 | 0.650 | 0.640 | | |
| II 68.5 | 0.568 | 0.570 | | |
| III 34.25 | 0.372 | 0.384 | | |
| IVc 24 | 0.250 | 0.232 | 0.239 | |
| Vc 17 | 0.192 | 0.186 | 0.185 | |
| VIc 13 | 0.140 | 0.130 | 0.135 | |
| VIIc 6 | 0.054 | 0.050 | 0.050 | 0.052 |

Patients suffering from schizophrenia showed a range of oxidase activity which overlapped the normal range considerably, a finding in agreement with that reported by Scheinberg and associates,[26] among others.[34,35] The results also indicate that there is a fairly wide range of serum oxidase activity in normal persons. In his paper reporting the finding of increased DPPD oxidase activity in the serum of mentally ill patients, Akerfeldt[36] suggested that this increase correlated with a low plasma ascorbic acid level, a suggestion that was confirmed by Angel[35] and Aprison and Grosz[37] among others.

However, criticisms have been made of Akerfeldt's technic,[38] and it must be noted that it differs a good deal from those used in the present investigation, especially in that a different substrate and a shorter time of incubation are used by Akerfeldt. Furthermore, the results presented in Table 4 indicate that, under the conditions described by the author, ascorbic acid has little or no effect on PPD oxidase activity of ceruloplasmin, a finding in agreement with that of Horwitt,[34] who noted that most of the ascorbic acid inhibition of serum oxidase activity is completed within a few minutes.

Finally, the results of measuring the serum copper in some 40 schizophrenic patients by Munch-Petersen,[39] which showed little difference from the normal range, appear to substantiate the suggestion that the increased oxidase activity in schizophrenics may be more apparent than real and due to the inherent limitations of the Akerfeldt procedure.

The following conclusions seem warranted by the results obtained in these investigations.

1. PPD oxidation is proportional to the amount of ceruloplasmin present in the serum.

2. A fairly wide range of serum oxidase activity exists in normal persons, which under the conditions of the test procedures described appears to be independent of the ascorbic acid content of the blood.

3. Many patients with various diseases have serum PPD oxidase activity within the normal range, though the average oxidase activity is higher in a group of such patients than the average in a group of normal persons.

4. Serum ceruloplasmin and serum PPD oxidase activity are uniformly low, and in most cases absent, with hepatolenticular degeneration (Wilson's disease).

5. The only other subjects in whom comparably low levels of ceruloplasmin and serum oxidase activity were found were newborn infants and patients with an untreated or refractory nephrotic syndrome who were losing considerable amounts of protein in the urine.

6. While no method of measuring ceruloplasmin or oxidase activity is immune to error, results are most consistent and most regularly reproducible with the second of the two enzymatic technics used in the present investigation, namely a modification of the procedure described by Boyd-Houchin.[31]

SUMMARY

A brief review of the significance of serum oxidase and ceruloplasmin is presented, and the available methods for measuring them in the blood are discussed.

Results of investigating two separate series of patients by different technics for measuring the serum PPD oxidase colorimetrically are presented.

It is concluded that more consistently reliable results are obtained with the second of these technics, practical details of which are described.

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# Treatment of epilepsy with *a*-ethyl-*a*-methylsuccinimide (P.M. 671)

Neil Gordon, M.D., M.R.C.P.

THE TREATMENT of epilepsy in its varied forms is still far from satisfactory in spite of the advances that have been made in recent years. This fact must stimulate the search for more effective medical treatment and is the reason for presenting this report of a trial of α-ethyl-α-methylsuccinimide in patients suffering from minor epilepsy. Favorable results have been recorded with the use of this drug in petit mal epilepsy. Zimmerman and Burgemeister[1] treated 109 patients with petit mal. An 85% reduction in attacks was obtained, but the best response was noted in the treatment of pure petit mal unassociated with any other type of attack. They found that side effects were infrequent and consisted only of drowsiness, dizziness, nausea, and gastric distress. Vossen,[2] in a trial of various succinimide derivatives, also found α-ethyl-α-methylsuccinimide particularly effective in the treatment of petit mal and better than any of the other allied drugs which he tried. Toxic reactions were never so troublesome that treatment had to be discontinued, but routine blood counts and urinalysis were recommended. Of the 60 patients treated by Lorentz De Haas and Stoel,[3] 34 responded satisfactorily. These authors stress that generalized seizures may also be controlled by this drug and conclude that the patients who are most likely to be freed of their fits are those with the highest intellectual levels, those treated at an early age, and those whose "absences" have been present for only a short period. Psychotic states developed in 3 of their patients during treatment.

In view of the encouraging reports of the use of α-ethyl-α-methylsuccinimide in minor epilepsy, it was decided to confine the trial to patients suffering from such seizures. Also, since in the beginning the supply of the drug was limited, the patients were selected because they had responded unsatisfactorily to all other treatment. This drug has at the moment been designated P.M. 671. So far, 28 patients have been treated for a sufficiently long period for preliminary conclusions to be drawn on the apparent efficacy of P.M. 671 (see table). The patients' response to the drug or combination of drugs immediately before the start of the trial was taken as a base line, and the results of the new treatment were classified as complete control (if the seizures stopped), 75% or more reduction, some reduction, no effect, and worse. P.M. 671 was in most cases added to the previous treatment or, if the patient had been given a combination of drugs, substituted for one of these. The dose varied from 250 mg. twice a day to 250 mg. five times a day. The treatment has so far been continued for periods varying between two weeks and one year, being stopped after a short interval only if the patient's condition was obviously deteriorating.

Petit mal epilepsy was diagnosed in 16 patients. The criteria for this diagnosis were the occurrence of brief interruptions of consciousness, often at frequent intervals, the absence of any evidence of brain damage, and the appearance in the electroencephalogram of outbursts of 3-cps spike and wave activity. In 6, there was complete control of the seizures. All were children under the age of 13, and their electroencephalograms showed outbursts of particularly regular 3-cps spike and wave activity. The number of attacks was reduced 75% or more in 2 patients. The electroencephalogram of 1 of these showed similar changes, but the other had atypical spike and wave activity at

From Booth Hall Children's Hospital, Manchester, England.

RESULTS OF TREATMENT WITH P.M. 671 IN 28 EPILEPSY PATIENTS

| *Diagnosis* | *Patients* | *Complete control* | *75% reduction* | *Some reduction* | *No change* | *Worse* | *Withdrawn from trial* |
|---|---|---|---|---|---|---|---|
| Typical petit mal | 14 | 6 | 1 | 6 | | | 1† |
| Petit mal with atypical electroencephalographic findings | 2 | | 1* | 1 | | | |
| Symptomatic petit mal (evidence of brain damage) | 8 | | | | 8 | | |
| Myoclonic epilepsy | 4 | | | | 2 | 2 | |

*Relapsed while on treatment but later improved again
†Child could not swallow capsules

4-cps. This patient relapsed while on treatment, although improving again after a brief period in hospital. In the case of 7 others, there was significant improvement but of a slightly lesser degree. All of these patients' electroencephalograms showed generalized spike and wave activity, but, in 1 patient who responded relatively poorly, this was of an atypical nature. Another had to stop taking P.M. 671 after four months owing to malaise and nausea. At the same time, there was an increase in the number of minor seizures. One child with petit mal could not be persuaded to swallow the capsules, which admittedly are of a large size for very young children to take.

A diagnosis of myoclonic epilepsy was made in the case of 4 patients. They also suffered from severer types of seizures, but the myoclonus was sufficiently troublesome to be a presenting symptom and P.M. 671 was added to the previous treatment in the hope that it would control these involuntary movements. The electroencephalograms of all these patients showed outbursts of irregular spike and wave activity, the paroxysmal discharges often being associated with the clinical manifestations of myoclonus. Unfortunately, P.M. 671 had no effect on the myoclonus in 2 of the patients, and the other 2 definitely became worse while on this treatment. In 1 of the former, the drug had to be stopped after a few weeks owing to the development of nausea and vomiting.

The remaining 8 patients were suffering from minor seizures consisting of brief interruptions of consciousness and, often, from major convulsions as well. However, there was strong presumptive evidence from their past histories, or from abnormal findings on examination suggesting brain damage, that the epilepsy was in fact of a symptomatic kind. For instance, several of the patients were mentally backward. Of this group, 7 showed paroxysmal outbursts of slow waves irregularly associated with spikes or sharp waves in their electroencephalograms, but in no case was this in the form of regular 3-cps spike and wave activity. In the remaining patient, the first electroencephalogram showed only a generalized dysrhythmia, but subsequent records demonstrated a temporal lobe focus and there was no doubt that this patient was suffering from the "pseudolapses" of temporal lobe epilepsy. P.M. 671 had no effect on the frequency of the seizures of any of these patients.

As far as these limited results are concerned, it appears that the role of P.M. 671 in the treatment of epilepsy is a restricted one. The incidence of major seizures has so far been unaffected, and the only attacks which were favorably influenced were those diagnosed as true petit mal. However, the response to treatment in this group was extremely satisfactory. It must be stressed that the patients were for the most part selected because they had failed to respond to other forms of treatment; no doubt, the over-all results would have been better if patients had been selected at random and if a greater number of those with petit mal had been included. The results stress the importance of restricting the term petit mal in the manner suggested and differentiating the various forms of minor epilepsy when carrying out a therapeutic trial of this nature.

Toxic symptoms in this series were conspicuous by their absence. Nausea and vomiting developed in 2 children, but no other adverse affects were noted; 1 patient became confused while on treatment, but this may have been an epileptic phenomenon and not due to the effect of drugs. Routine blood

counts were done but never showed any abnormalities.

It was considered that the results of the treatment of petit mal with $\alpha$-ethyl-$\alpha$-methylsuccinimide were sufficiently encouraging to warrant this report. There seemed to be little doubt that, in this particular variety of epilepsy, it had a most beneficial effect combined with a low toxicity, qualities that are eagerly sought for by anyone engaged in treatment of petit mal. It can only be hoped that the initial promise of this drug will be maintained when longer trials have been completed. The ultimate prognosis for the cessation of petit mal epilepsy may be relatively good, but the seizures often bring considerable distress to the patients and, as they are almost always children, to an even greater extent to their parents.

The author wishes to thank Parke, Davis and Company for making a supply of P.M. 671 available for use in this trial.

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# Training program in Pediatric Neurology

THE INCREASING INTEREST of potential candidates in the field of pediatric neurology challenges the two American Boards most concerned to determine guidelines for program directors in pediatrics and in neurology and for potential candidates in these disciplines. The Committees on Child Neurology of the American Board of Pediatrics and the American Board of Psychiatry and Neurology met on September 21, 1959, and October 21, 1960, and submitted to their respective boards the following statement:

Recommendations for a desirable training program in Pediatric Neurology:

1. A year of approved internship.

2. Approved residency training in a pediatric service meeting established requirements of the American Board of Pediatrics.

3. Two years of residency training in general neurology, including the basic neurologic sciences, under conditions consistent with established requirements of the American Board of Psychiatry and Neurology.

4. A year of residency training in a pediatric neurology service meeting the established requirements of the American Board of Psychiatry and Neurology.

Flexibility should be allowed in the order in which these components of the training program are taken.

TRAINING PROGRAM FACILITIES

1. The pediatric neurology service should be in the setting of an active pediatric service, with a sufficient number of beds for the number of residents in training, and an active outpatient department. It is also recommended that there be opportunities for the trainee to study the newborn and that he also have an opportunity to maintain continuing contact with patients in this category.

2. The pediatric neurology service should be under qualified neurologic direction.

3. Patient beds assigned to the pediatric neurology service should preferably be in close physical contact with the pediatric service and under independent pediatric neurologic direction.

4. The pediatric neurology resident should have responsibility under competent supervision for patient care.

5. It is also desirable that the pediatric neurology program be in a setting in which basic neurologic science contacts are readily available.

The adoption of these recommendations might quite conceivably serve as a preliminary step toward further consideration of a formalized subspecialty board in pediatric neurology.

JOHN MCK. MITCHELL, M.D.
Executive Secretary
American Board of Pediatrics, Inc.

DAVID A. BOYD, JR., M.D.
Executive Secretary-Treasurer
American Board of Psychiatry and Neurology, Inc.

# Program of the American Academy of Neurology

## *Thirteenth Annual Meeting*

**April 24-29, 1961**

**Sheraton-Cadillac Hotel, Detroit**

## General Scientific Session

**Morning Meeting, 9 A.M., Thursday, April 27, 1961**

**Grand Ballroom**

*Chairman:* Augustus S. Rose, *Los Angeles*

*Secretary:* Robert A. Utterback, *Memphis*

**Presidential Address**
Augustus S. Rose, *Los Angeles*

**Muscular Dystrophy Sensitive to Curare**
R. T. Ross, *Winnipeg*

**Characteristics of Block of Neuromuscular Transmission Produced by Various Drugs in Animals and Their Relationship to Myasthenic Syndromes in Man**
Michael M. Okihiro and Edward H. Lambert, *Rochester, Minn.*

**Evidence for Immunological Factors Having Possible Etiologic Significance in Myasthenia Gravis**
William L. Nastuk, *New York City*

**The Preclinical Detection of Muscular Dystrophy by Serum Enzyme Elevations**
Carl M. Pearson, S. R. Chowdhury, William M. Fowler, Jr., and Margaret H. Jones, *Los Angeles*

**A Behavioral Method to Study Pain Perception in Monkeys—Effects of Some Pharmacological Agents**
Elliot D. Weitzman and Gilbert S. Ross, *Washington, D. C.*

**Physiological and Behavioral Effects of Caudate Deficit in the Albino Adult Rat**
J. R. Whittier, A. Orr, F. CoTue, and L. Goldschmidt

**Neurological Manifestations of Hypomagnesemia**
Robert A. Fishman, *New York City*

**Central Inhibitory Components of the Aldosterone Regulating System**
Anna N. Taylor and Gordon Farrell, *Cleveland*

**Influence of Hormones on Recovery of Electrical Activity of Crushed Sciatic Nerve in Hypophysectomized Rats**
L. Soskind, A. V. Boccabella, and P. J. Harman, *Jersey City, N. J.*

## Afternoon Meeting, 1:30 P.M., Thursday, April 27, 1961

**Grand Ballroom**

*Chairman:* Benedict Nagler, *Colony, Va.*

*Secretary:* Kenneth Magee, *Ann Arbor, Mich.*

**Effects of Oral Methaminoazepoxide (Librium) on Seizures and Electroencephalographic Abnormalities of Various Form and Cause**
C. Wesley Watson, Reinette Bokwer, and Claire Bernstein, *Boston*

**Convulsions Following Ingestion of a Plastic Explosive**
Richard Satran, *Ann Arbor, Mich.*

**Effect of Drugs on Secondary Epileptogenic Lesions**
Frank Morrell and Lowell Baker, *Minneapolis*

**The Relationship Between Psychological Test Patterns and Electroencephalographic Findings in Patients with Temporal Lobe Seizures**
Brenda Milner and Richard L. Rovit, *Montreal*

**"Seizures" Related to Spinal Cord and Root Pathology**
Morton Nathanson, *New York City*

**Myoclonic Epilepsy of Unverricht-Lundborg (Meul)**
Francis Kruse, Jr., *Lackland Air Force Base, Tex.*

**Studies of Eastern Encephalitis**
Richard A. Chambers and Gerald S. Levey, *Jersey City, N. J.*

**Trypan Red and Blood-Brain Barrier Permeability in Neurotropic Virus Disease**
Benjamin V. Siegel, W. W. Anderson, and Robert B. Aird, *San Francisco*

**Effects of iodinized Contrast Media upon Blood Electrolytes, Proteins and Red Cells**
Henn Kutt, Thomas Milhorat, and Fletcher McDowell, *New York City*

**The Use of $I^{131}$ Labeled Iodoantipyrine in the Determination of Rapid Changes in Cerebral Blood Flow**
O. M. Reinmuth and Peritz Scheinberg, *Miami*

**Spontaneous Intracranial Hemorrhage: A Clinical, Radiographic and Pathological Analysis of 350 Cases**
Herbert G. Vaughan, Jr., and Mark C. Levine, *New York City*

**Clinical Trail of Fibrinolytic Enzymes in the Treatment of Cerebral Thrombosis**
B. H. Smith, P. Giannopoulos, J. L. Ambrus, and H. W. Gillen, *Buffalo, N. Y.*

**Treatment of Cerebral Thrombo-Embolism by Fibrinolysin**
F. A. Elliott, *Philadelphia*

**Fibrinolysis and the Central Nervous System**
Stuart A. Schneck and Kurt N. von Kaulla, *Denver*

## Afternoon Meeting, 1:30 P.M., Friday, April 28, 1961

(General Scientific Session in conjunction with Child Neurology Section)

**Grand Ballroom**

*Chairman:* Charles A. Kennedy, *Philadelphia*

*Secretary:* Gordon Millichap, *Boston*

**S. Weir Mitchell Award Essay**
*Subject and author to be announced*
This is the annual award given by the Woman's Auxiliary to the American Academy of Neurology to the junior member who has submitted the manuscript adjudged best by the committee.

**Arteriovenous Malformation of the Vein of Galen in Children**
Arnold P. Gold, Sidney Carter, and Joseph Ransohoff, *New York City*

**Congenital Universal Indifference to Pain with Absence of Sweating in Male Siblings**
August G. Swanson, *Seattle*

**A Study of the Formation of Subdural Effusions Using Radioactive $I^{131}$ Human Serum Albumin**
Edward F. Rabe, Robert E. Flynn, and Philip R. Dodge, *Boston*

**Acute Cerebellar Ataxia in Children Associated with Infection by Poliovirus I**
D. Méndez-Casion, Luis P. Sánchez-Longo, and Marta Valcárcel, *Puerto Rico;* Leon Rosen, *Washington, D. C.*

**Histology of the Brushfield Spot**
Joseph H. French and David B. Clark, *Baltimore*

**Prognosis of Convulsions and Twitching in the Newborn**
Matthew E. Graham and John S. Prichard, *Toronto*

**An Evaluation of the Moro Reflex**
Milton Westphal and Charles Kennedy, *Philadelphia*

**The Nature of the Plantar Response in Infancy**
Thomas E. Twitchell, *Boston*

## Morning Meeting, 9:00 A.M., Saturday, April 29, 1961

**Grand Ballroom**

*Chairman:* Knox H. Finley, *San Francisco*

*Secretary:* John T. Mc Henry, *Detroit*

**Compressive Spinal Cord and Root Syndromes in Achondroplastic Dwarfs**
Roger C. Duvoisin, *Lackland Air Force Base, Tex.*, and Melvin D. Yahr, *New York City*

**Hereditary Interstitial Nephritis Associated with Polyneuropathy**
Oscar Marin and M. Richard Tyler, *Boston*

**Dopamine and Basal Ganglia Diseases**
Andre Barbeau, G. F. Murphy, and T. L. Sourkes, *Montreal*

**Electromyographic Study of Reciprocal Innervation in Blinking**
Maurice W. Van Allen and Frederick C. Blodi, *Iowa City, Iowa*

**Robert Wartenberg Memorial Lecture**
*To be announced*

**Patterns of Brain-Stem Dysfunction Resulting from Supratentorial Lesions in Man**
D. E. McNealy and Fred Plum, *Seattle*

**The Ability to Distinguish Two Cutaneous Stimuli Separated by a Brief Time Interval: A Parietal Lobe Function**
J. B. Green, C. L. Reese, J. J. Pegues, and F. A. Elliott, *Philadelphia*

**After-Extinction as a Phenomenon of Partially Recovered Parietal Infarction**
S. Horenstein and J. H. Gardner, *Boston*

**Paroxysmal Familial Chorea Athetosis**
Jonathan Williams and Harold Stevens, *Washington, D. C.*

**Muscle Blood Flow Studies in Tension Headaches**
Yusaf Onel, A. P. Friedman, and J. Grossman, *New York City*

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# Section of Neuroanatomical Sciences

## Afternoon Session, 2 P.M., Thursday, April 27, 1961

**Crystal Ballroom**

*Chairman:* Orville T. Bailey, *Chicago*

*Secretary:* Ray S. Snider, *Chicago*

**Ultrastructure of Cerebellum with Special Reference to Synaptic Mitochondria**
Charles H. Good, *Minneapolis*

**Combined Studies of Human Cerebral Biopsies**
A. Biochemistry: S. R. Korey, R. D. Terry, C. J. Gomez, M. Rayport, and L. Scheinberg, *New York City*
B. Ultrastructure: R. D. Terry, L. Scheinberg, S. R. Korey, M. Rayport, and C. J. Gomez, *New York City*

**Neuropathological Observations in Maple Syrup Urine Disease**
Jacobo Silberman, Joseph Dancis, and Irwin Feigin, *New York City*

**Electron Microscopic Observations on Experimental Rodent Polioencephalitis (MM Strain)**
Erland Nelson, *Minneapolis;* Hermann Hager and Ernest Kovacs, *Munich, Germany*

**Immunization to Transplantable Mouse Glioma**
Labe C. Scheinberg and Mark C. Levine, *New York City*

**Histochemical Demonstration of RNA in Oligodendroglia**
Harold Koenig, *Chicago*

**The Anatomical Basis for Paracusis Willisiana**
M. Wharton Young, *Washington, D. C.*

**The Innervation of the Spinal Dura Mater and the Dura Mater of the Posterior Cranial Fossa by Branches of Spinal Nerves**
Donald L. Kimmel, *Chicago*

**Neural Correlates of the Vestibulo-Ocular Reflex**
A. B. Scheibel, C. H. Markham, and R. Koegler, *Los Angeles*

**Morphological Findings in Studies of Regeneration of Synapses in the Mammalian Spinal Cord**
C. C. Turbes, *Lafayette, Ind.*, and L. W. Freeman, *Indianapolis*

## Section of Neuroanatomical Sciences

### Morning Meeting, 9 A.M., Friday, April 28, 1961

Crystal Ballroom

SYMPOSIUM – HYPOTHALAMUS

*Chairman:* Ray S. Snider, *Chicago*

**Anatomy**
W. R. Ingram, *Iowa City, Iowa*

**Neuroendocrine Aspects**
Seymour Reichlin, *St. Louis*

**Control of Gonadotropins and Sexual Behavior**
C. H. Sawyer, *Los Angeles*

**Single Neurone Activity**
John Green and Barry Cross, *Los Angeles*

**Behavioral Aspects**
John Knott, *Iowa City, Iowa*

**Electron Microscopic Observations in Normal and Altered Physiological States**
Sarah Luse, *St. Louis*

**Summation**
H. W. Magoun, *Los Angeles*

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## Section of Neurochemistry

### Morning Meeting, 9 A.M., Friday, April 28, 1961

Grand Ballroom

*Chairman:* Donald B. Tower, *Bethesda, Md.*

*Secretary:* Maynard M. Cohen, *Minneapolis*

**Factors Affecting Lactic Dehydrogenase and Glutamic Oxalacetic Transaminase Activity in Spinal Fluid**
Hartwell G. Thompson, Jr., and Herbert Spolter, *Madison, Wis.*

**Simultaneous Studies of the Arterial Blood and CSF Acid-Base Balance Ionic Distributions, Water and Osmolarity Concentrations in Man**
Robert G. Fisher and George H. Stueck, Jr., *Hanover, N. H.*

**Glutamic Acid Decarboxylase Activity in Developing Brain**
Williamina A. Himwich and Juanita Graves, *Galesburg, Ill.*

**Interrelationship of Glucose, Glutamate and Aspartate Metabolism in Rat Cerebral Cortex in Vitro**
E. B. Chain, *Rome;* M. M. Cohen, *Minneapolis;* F. Pocchiari, *Rome*

**Determination of Protein Fractions in Muscle Biopsy Samples**
Karl G. Henriksson, Beni Horvath, and Joseph B. Proctor, *Bethesda, Md.*

**INTERMISSION**

**The Amino Acid Composition of Proteolipid Proteins**
Frederick Wolfgram and Augustus S. Rose, *Los Angeles*

**Brain Lipids in Multiple Sclerosis and Other Diseases**
B. Gerstl, J. K. Smith, M. Tavaststjerna, and R. B. Hayman

**Aminoglycolipids and Glycoproteins of Brain in Neuropsychiatric Disorders**
Samuel Bogoch, *Boston*

**The Lipid Profile of Cerebrospinal Fluid in Various Diseases, Especially Multiple Sclerosis**
Wallace W. Tourtellotte, Sonia Janich, Karen Gustafson, John F. Somers, and Russell N. DeJong, *Ann Arbor, Mich.*

## READ BY TITLE

**Clinical Significance of the EEG in Blind Children**
J. Cohen, L. D. Boshes, and R. S. Snider, *Chicago*

**Epilepsy in Multiple Sclerosis**
William E. Drake and Donald Macrae, *San Francisco*

**Chylomicron Index in Demyelinating Diseases**
Clinton H. Thienes, *Pasadena, Calif.*

**Functional Separation of Carotid and Vertebral Circulation in the Dog**
Williamina A. Himwich, *Galesburg, Ill.*

**Effect of Bilateral Auditory Cortex Ablation of PGSR Audiometry in Cats**
William T. McLean, Jr., *Philadelphia*

**Focal Cortical Encephalopathy Produced by Pyrimidine Analogs**
Harold Koenig, I. James Young, and LeRoy Kurth, *Chicago*

**Studies of Cerebral Blood Flow with the Dye Dilution Techniques**
A. Iannone, *Minneapolis*

**Anticoagulant Therapy in Ischemic Cerebrovascular Disease: Long-Term Follow-Up and Present Status**
Robert G. Siekert, Clark H. Millikan, and Jack P. Whisnant, *Rochester, Minn.*

**Lethal Factors in Patients with Strokes**
Robert N. Baker, Uwamie Tomiyasu, Wilbur Schwartz, Harry C. H. Fang, and Augustus S. Rose, *Los Angeles*

---

## SCIENTIFIC EXHIBITS

**The Motor Manifestations of Epileptic Seizure Patterns—A Photographic Analysis**
E. Rodin, *Detroit*

**Cerebrovascular Disease: Approach to Diagnosis and Management**
E. S. Gurdjian, D. W. Lindner, W. G. Hardy, M. Croll, L. M. Thomas, S. J. Figiel, J. E. Lofstrom, J. E. Webster, and J. L. Whelan

**Experimental Epilepsy in Rabbits**
G. Nellhaus

**The Effect of One Individual on Another**
W. H. Gantt, J. E. O. Newton, and F. L. Royer

**The Hoover Sign: An Objective Sign of Pain and/or Weakness in the Back or Lower Extremities**
A. J. Arieff, W. A. Larmon, E. L. Tigay, and J. F. Kurtz

**Measurement of Rigidity, Strength and Tremor in Parkinson's Disease**
D. D. Webster, C. Doering, and S. Tremayne

**Collateral Circulation in Extracranial Vascular Occlusion**
W. S. Fields, W. G. Lucas, E. S. Crawford, and M. E. DeBakey

**Intracranial Cerebral Herniations**
O. Solnitzky

**Heller's Disease—A Clinico-Pathological Study**
L. Liss and H. Knobloch

**Autotomography Showing the Normal and Pathological Midline Ventricular Structures and Basal Cisterns**
M. M. Schecter and C. G. de Gutierrez-Mahoney

**Myasthenia Gravis—Evaluation of Diagnostic Techniques**
K. E. Osserman, G. Genkins, R. Mones, P. Kornfeld, E. Cohen, P. Anderson, A. Strauss, and L. I. Kaplan

**A Program of Management and Rehabilitation for the Quadriplegic**
E. P. Roemer

**Anatomical Changes in Cerebral Vascular Disease**
U. Tomiyasu and R. N. Baker

**A Study of Warning, Gainful Employment and Behavior Patterns in Epilepsy**
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***References:*** **1.** Dorfman, W.: The New Approach to Depression, WORLD-WIDE ABSTRACTS OF GENERAL MEDICINE 2:10 (November) 1959. **2.** Dickel, H. A., *et al.*: Tension Fatigue States and Their Adjunctive Treatment Using Nardil, CLINICAL MED. 6:1579 (September) 1959. **3.** Sainz, A.: The Phrenopraxic Activity of a Non-noxious Antidepressant, ANN. NEW YORK ACAD. SC. *80*:780-789 (September) 1959. **4.** Nardil Package Brochure (October) 1960. **5.** Furst, W.: Psychopharmacological or Electrical Therapy of Severe Endogenous Depression, J. M. SOC. NEW JERSEY *57*:3 (March) 1960.

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# REVIEW COURSES IN BASIC and CLINICAL NEUROLOGY

## April 24, 25, 26, 1961

***Preceding the***

## 1961 AMERICAN ACADEMY OF NEUROLOGY MEETING

**Sheraton-Cadillac Hotel, Detroit, Michigan**

**NEUROPATHOLOGY**—April 24, 1961. Dr. Erland R. Nelson. Fees: Juniors: $20.00; Fellows, Actives and Associates: $25.00; Non-members: $30.00. Deposit on slide box: $25.00 (all membership categories).

**BASIC ELECTROENCEPHALOGRAPHY**—April 24, 1961. Dr. Fernando Torres. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

**NEUROCHEMISTRY**—April 24, 1961. Dr. Maynard M. Cohen and Dr. Donald B. Tower. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

**METABOLIC DISORDERS OF THE NERVOUS SYSTEM**—April 24, 1961. Dr. Gilbert H. Glaser. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

**ADVANCED CHILD NEUROLOGY**—April 25, 1961. Dr. Michael E. Blaw and Dr. Paul M. Ellwood, Jr. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

**THE ELECTRON MICROSCOPE AND THE NERVOUS SYSTEM**—April 25, 1961. Dr. Augustus S. Rose. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

**NEWER CONCEPTS OF HUMAN CEREBRAL ORGANIZATION**—April 25, 1961. Dr. John S. Meyer. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

**NEURORADIOLOGY**—April 25, 1961. Dr. A. L. Sahs. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

**ABNORMAL STATES IN NEUROPHYSIOLOGY**—April 26, 1961. Dr. James L. O'Leary. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

**ADVANCED ELECTROENCEPHALOGRAPHY**—April 26, 1961. Dr. Frank Morrell. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

**MEDICOLEGAL ASPECTS OF NEUROLOGY**—April 26, 1961. Dr. Royal C. Gray. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

In addition a special review course in Common Neurologic Diseases is offered to General Practitioners on Wednesday, April 26, 1961. The registration fee is ten dollars. Credit will be given by the American Academy of General Practice. This course is not available to members of the American Academy of Neurology. Dr. Benjamin Boshes is Course Chairman.

**ENROLLMENT FOR ALL COURSES IS LIMITED**

**Priority will be determined by date of application.**
**No application will be accepted after April 14, 1961.**

*Applications will not be taken at the Sheraton-Cadillac Hotel in Detroit.*

Outline of each course, application and further information may be obtained from

**SPECIAL COURSES – AMERICAN ACADEMY OF NEUROLOGY**
**4307 East 50th Street, Minneapolis 17, Minnesota**

# NEWSLETTER

AMERICAN ACADEMY OF NEUROLOGY

MARCH 1961

Augustus S. Rose, M.D., President
A. L. Sahs, M.D., President-Elect
Joseph M. Foley, M.D., Vice-President
Robert Utterback, M.D., Secretary
Charles M. Poser, M.D., Treasurer

---

**Special AAN Courses to Reach New High**

Chairman A. B. Baker of the AAN Special Courses Committee announces that the review courses at the Thirteenth Annual AAN Meeting in Detroit's Sheraton-Cadillac Hotel (April 24 through 26) will exceed all previous ones in breadth and depth; 4 of the more popular courses given in the past — neuropathology (Erland R. Nelson), neurochemistry (Maynard M. Cohen and Donald B. Tower), basic EEG (Fernando Torres), and neuroradiology (A. L. Sahs) — are to be repeated. But, as expansions of the basic courses, there will be new courses in advanced EEG (Frank Morrell) and advanced child neurology (M. E. Blaw and P. M. Ellwood, Jr.) which will present more advanced material in these fields. Then there will be 5 entirely new courses in basic and clinical neurology, abnormal states in neurophysiology (James L. O'Leary), newer concepts of human cerebral organization (John S. Meyer), and the electron microscope and the nervous system (Augustus S. Rose). The new courses in clinical neurology comprise medical-legal aspects of neurology (Royal C. Gray) and metabolic defects of the nervous system (Gilbert H. Glaser).... Chairman Baker urges early registration for these courses. No applications will be accepted after Friday, April 14, and no registrations will be accepted at the Sheraton-Cadillac Hotel in Detroit. All communications relating to these special courses should be addressed to American Academy of Neurology, 4307 E. 50th Street, Minneapolis 17, Minn. The registration fees for all courses except neuropathology are $10 for juniors; $15 for fellows, actives, and associates; and $20 for nonmembers. The registration fee for neuropathology is $20 for juniors; $25 for fellows, actives, and associates; and $30 for nonmembers.... Benjamin Boshes will give his proverbial popular course in neurology for the general practitioner. Registration in this course, not open to AAN members, is by special application. The fee is $10.

**Bronk Elected to Brazilian Academy**

Detlev Bronk, President of the Rockefeller Institute and of the National Academy of Sciences, has been elected an honorary member of the Brazilian Academy of Science and at a special University convocation was made an Honorary Doctor of the University of Brazil. Dr. Bronk recently made an extensive trip through Brazil to advise on the development of science in that country as a basis of its industrial development.

**New Diplomates in Neurology** At the Annual Meeting of the American Board of Psychiatry and Neurology held in New York December 10 through 13, 1960, 9 candidates, as a result of the examinations, were certified in neurology: M. P. Goodson (Miami); R. S. Jampel (Brooklyn); H. R. Karp (Atlanta); N. J. A. Keller (Washington, D.C.); W. R. Kinkel (Tonawanda, N. Y.); N. L. Low (New York); J. G. Millichap (Rochester, Minn.); I. Rapin (New York); and O. M. Reinmuth (Miami).... In 1961, the Board will hold 3 examinations: New Orleans, March 20 and 21; Chicago, October 9 and 10; and New York, December 11 and 12.... Effective January 1, 1962, the following fee schedule will be adopted: Application fee: $75; examination fee: $100; reexamination fee (complete reexamination): $100; reexamination fee (1 or 2 subjects): $75.... All communications and inquiries should be sent to Dr. David A. Boyd, Jr., Executive Secretary-Treasurer, American Board of Psychiatry and Neurology, 102-110 Second Avenue, S. W., Rochester, Minn.

**Cerebrovascular Conference Again Staged at Princeton** The environs of the Princeton campus were again the scene of a Third Cerebrovascular Disease Conference, this time sponsored by the American Neurological Association, the American Heart Association, and the National Institute of Neurological Diseases and Blindness (January 4 through 6, 1961). After introductory remarks by Clark H. Millikan, the conferees proceeded to consider and discuss the diagnostic, pathogenic, and treatment aspects of three major manifestations of cerebrovascular disease: incipient or impending stroke, progressing stroke, completed stroke and completed stroke with evidence of more activity. The sessions were closed by remarks by H. G. Wolff. Among the neurologists participating were R. D. Adams, R. N. Baker, S. B. Carter (Middlesex, England), D. E. Denny-Brown, Harry Fang, W. S. Fields, C. M. Fisher, A. Heyman, H. Karp, Fletcher McDowell, H. H. Merritt, J. S. Meyer, A. L. Sahs, Peritz Scheinberg, R. G. Siekert, J. F. Toole, and Charles E. Wells.

**MGH Inaugurates Anniversary Year** Statesmen from the United States and scientists from around the world joined in panel discussions and scientific symposia to honor the One Hundred and Fiftieth Anniversary of the Massachusetts General Hospital in Boston (January 31 through February 2). Mr. John E. Lawrence, Trustee of the Hospital, was chairman of the committee that developed the convocation around the theme "To Heighten the Hope of Man." Paul Dudley White was chairman of the Doctors' Committee planning the scientific symposia. A formal anniversary banquet for scientists, physicians, and statesmen climaxed the convocation on Thursday evening, February 2. A notable array of scientists, physicians, and statesmen participated in the timely

discussions and symposia. A highlight in the convocation was a scientific symposium on "The Study of Cell Structure in Nervous Diseases — Quantitation in Neuropathology," under the direction of Raymond D. Adams, Chief of Neurology Service and Neuropathologist, Massachusetts General Hospital, and Bullard Professor of Neuropathology at Harvard University. Among the participants were Paul Yakovlev, Clinical Professor of Neuropathology at Massachusetts General Hospital and Curator of the Warren Anatomical Museum, Harvard University; Ludo van Bogaert, Director of Institut Bunge, Antwerp, and President of the World Federation of Neurology; Jan Cammermayer, Chief of Section of Experimental Neuropathology, NINDB; and Oliver H. Lowry, Professor of The Edward Mallinckrodt Department of Pharmacology, Washington University School of Medicine, St. Louis.

**Houston Neurological to Hold Symposium** Under the direction of Edmund M. Fountain (Program Chairman) and William S. Fields (Symposium Chairman), the Houston Neurological Society and the Department of Neurology of Baylor University College of Medicine will conduct a symposium on the biology and treatment of intracranial tumors March 9 through 11, 1961. The scientific sessions, which will be held in the Jesse H. Jones Library Building of the Texas Medical Center, will feature the epidemiology and pathogenesis of intracranial tumors (O. T. Bailey, Chicago, Moderator) and the histochemistry and pathology of glial neoplasms (William S. Fields, Houston, Moderator). There will also be special presentations devoted to modern diagnostic methods and therapeutic procedures, including the treatment of brain tumors in children; 16 eminent authorities in the United States and 2 from abroad, Jean Bouchard (Montreal) and Isaac Costero (Mexico City), will participate in the symposium.... The Society's annual banquet will be held in the Emerald Room of the Shamrock Hilton Hotel on Friday, March 10.... Communications and inquiries should be sent to Dr. Paul C. Sharkey, Houston Neurological Society, 1200 M. D. Anderson Boulevard, Texas Medical Center, Houston 25.

**Millikan Named President of ARNMD** At the Executive Sessions of the Fortieth Annual Meeting of the Association for Research in Nervous and Mental Disease in New York (December 9 and 10, 1960), Clark Millikan was elected President and Chairman of the 1961 Commission, ARNMD. Elected as Vice-Presidents were Seymour S. Kety, recently appointed as Professor of Psychiatry at the Johns Hopkins Hospital, and Irving S. Wright (New York). The topic for the 1961 ARNMD meeting at the Hotel Roosevelt in New York City (December 8 and 9, 1961) is Cerebrovascular Disease. ARNMD Secretary-Treasurer is Rollo J. Masselink, 700 West 168th Street, New York 32.

**Deadline for Abstracts American EEG Society** Program Chairman Frank Morrell warns (second notice) that the deadline for abstracts for the Atlantic City meeting of the American EEG Society (June 8 through 11, 1961) is March 15, 1961. Each abstract should not exceed 200 words and should be submitted in triplicate to the Program Chairman, indicating the type of equipment needed for presentation. The program committee consists of Frank Morrell, Richard P. Schmitt, and Fernando Torres.... All abstracts should be mailed to Dr. Frank Morrell, Program Chairman, Division of Neurology, State Medical Center, Palo Alto, Calif.

**American Neurological Association to Meet in Atlantic City** The Eighty-sixth Annual Meeting of the American Neurological Association will be held at the Claridge Hotel in Atlantic City June 12 through 14. The scientific sessions will be on the morning and afternoon of Monday, June 12, and Tuesday, June 13; there will be a morning session only on Wednesday, June 14. The annual dinner will be held on Tuesday, June 13. Members applying for a place on the program should submit to the Secretary, before March 15, 1961, a program abstract not exceeding 1,000 words, for publication in the Transactions. Abstracts should be sent in duplicate and separate from letters of transmittal. The Secretary will inform members as soon as possible after March 15, 1961, of the decision of the Program Committee on the acceptability of titles. All communications and inquiries should be sent to Dr. Melvin D. Yahr, ANA Secretary, Neurological Institute, 710 W. 168th Street, New York 32. Nonmembers may read papers of special interest by special invitation of the Program Committee.... On Monday evening, June 12, the ANA will hold a joint symposium with the American Association of Neuropathologists on "Properties of Membranes and Their Relationship to Diseases of the Nervous System." The program of this symposium is limited to invited speakers and discussants.

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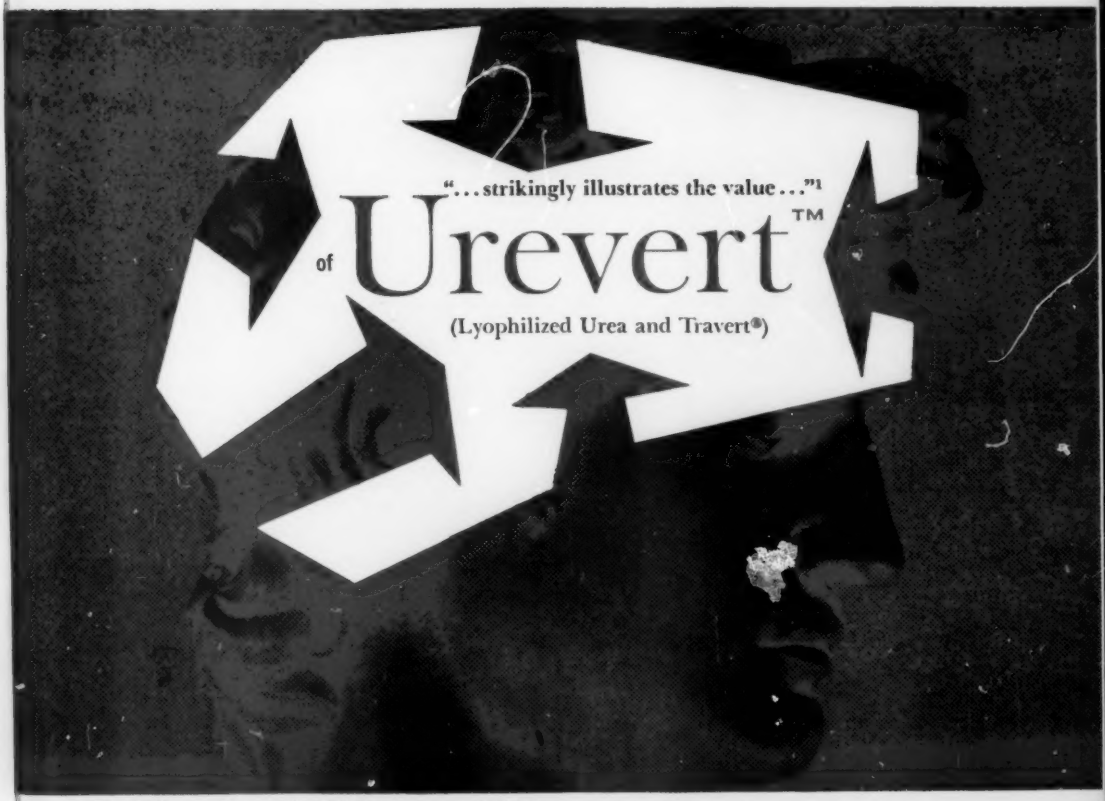


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1. Taheri, Z. E.: Urevert in Cranial Trauma and Brain Surgery, J. Internatl. College of Surgeons *32*:389 (Oct.) 1959.
2. Javid, M.: Urea—New Use of an Old Agent, Reduction of Intracranial and Intraocular Pressure, The Surgical Clinics of North America, Philadelphia, W. B. Saunders Company, Aug. 1958, p. 907.

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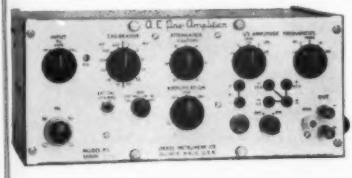

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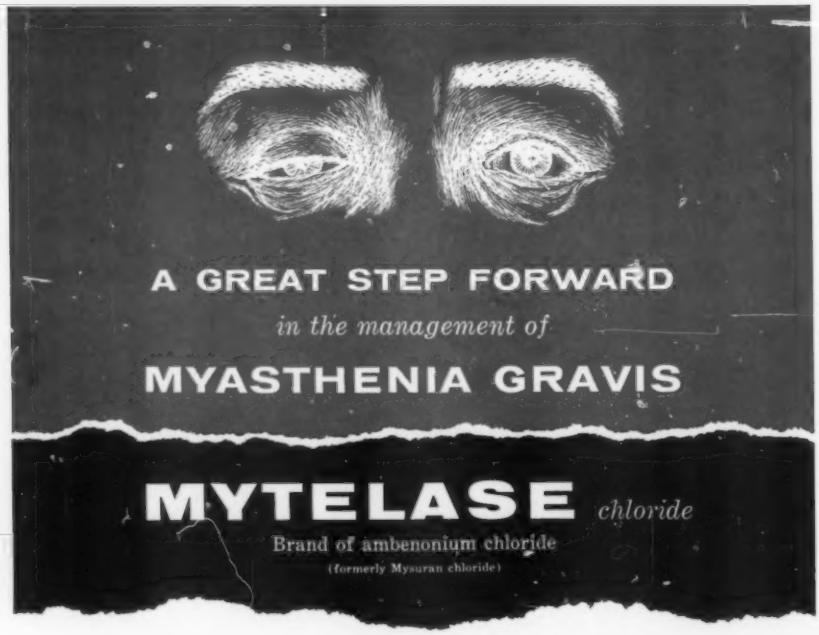


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1. Schwab, R.S.; Marshall, Clare K.; and Timberlake, William: *J.A.M.A.*, 158:625, June 25, 1955.
2. Schwab, R.S.: *Am. Jour. Med.*, 19:734, Nov., 1955.

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